Handheld photoacoustic imaging and sensing for 3D medical visualization

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HANDHELD PHOTOACOUSTIC IMAGING AND SENSING FOR 3D MEDICAL VISUALIZATION

LIU SIYU

School of Electrical & Electronic Engineering

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2019

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarised materials, and has not been submitted for a higher degree to any other University or Institution.

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Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it is free of plagiarism and of sufficient grammatical clarity to be examined. To the best of my knowledge, the research and writing are those of the candidate except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Kim Tae Hyung

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Authorship Attribution Statement

This thesis contains materials from 6 papers published in the following peer-reviewed journals, and 1 paper accepted in a conference in which I am listed as an author.

Sub-section 2.1 in Chapter 2 is published as “S. Liu, R. Zhang, Z. Zheng, and Y. Zheng, Electromagnetic–Acoustic Sensing for Biomedical Applications, Sensors, 2018. DOI: 10.3390/s18103203 (Invited review paper)”.

The contributions of the co-authors are as follows:

- Assoc Prof Zheng Yuanjin provided the initial project direction and edited the manuscript drafts.
- I prepared the manuscript drafts.
- The manuscript was revised by Ms. Zhang and Mr. Zheng.

Sub-section 2.3.5 in Chapter 2 is published as “S. Liu, X. Feng, F. Gao, H. Jin, R. Zhang, Y. Luo, and Y. Zheng, GPU-accelerated two-dimensional synthetic aperture focusing for photoacoustic microscopy, APL Photonics, 2018. DOI: 10.1063/1.5005145”.

The contributions of the co-authors are as follows:

- Assoc Prof Zheng Yuanjin provided the initial project direction and edited the manuscript drafts.
- I prepared the manuscript drafts. The manuscript was revised by Dr. Feng and Dr. Gao.
- I designed the imager system. Dr. Jin, Ms. Zhang, Ms. Luo, and Mr. Zheng assisted in experimental demonstration.

Chapter 3 is published as “S. Liu, X. Feng, H. Jin, R. Zhang, Y. Luo, Z. Zheng, F. Gao, and Y. Zheng, Handheld photoacoustic imager for theranostics in 3D, IEEE Transactions on Medical Imaging, 2019. DOI: 10.1109/TMI.2019.2900656”.

The contributions of the co-authors are as follows:

- Assoc Prof Zheng Yuanjin provided the initial project direction and edited the manuscript drafts.

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- I designed the imager system. Dr. Jin, Ms. Zhang, Ms. Luo, and Mr. Zheng assisted in experimental demonstration.

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- Assoc Prof Kim Tae Hyoung and Assoc Prof Zheng Yuanjin provided the initial project direction and edited the manuscript drafts.
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The contributions of the co-authors are as follows:

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- I prepared the manuscript drafts.
- Dr. Feng designed the sensing system. Ms. Zhang assisted in experimental demonstration.

Chapter 6 is published as “S. Liu, K. Tang, X. Feng, H. Jin, F. Gao, Y. Zheng, Towards wearable healthcare: a miniaturized 3D imager with coherent frequency domain photoacoustics, IEEE Transactions on Biomedical Circuits and Systems, 2019. DOI: 10.1109/TBCAS.2019.2940243”.

The contributions of the co-authors are as follows:

- Assoc Prof Zheng Yuanjin provided the initial project direction and edited the manuscript drafts.

- I prepared the manuscript drafts.
- I designed the imager system. Dr. Tang designed the laser driver circuit. Dr. Feng, Dr. Gao, and Dr. Jin assisted in experimental demonstration.

16-July-2019

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This Ph.D. thesis is a summarization of my four-year research journey from being a curious youth (knowledge receiver) to become an almost independent researcher (research producer). During this period, though with ups and downs, I cherish every single moment and every person who accompanies me through this wonderful journey. Inasmuch as this may be the only opportunity to express my heartfelt gratitude in write, I may be a little bit more verbose than necessary.

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Table of Contents

Statement of Originality	II
Supervisor Declaration Statement.....	III
Authorship Attribution Statement.....	IV
Acknowledgments	VII
Table of Contents	IX
Summary	XII
List of figures.....	XIV
List of tables	XVI
Chapter 1. Introduction	1
1.1. Overview of the Photoacoustic Technique	1
1.2. Motivation and Objectives	5
1.3. Major Contributions.....	9
1.4. Organization of the Thesis	10
Chapter 2. Photoacoustic Imaging: Theories, Implementations and Reconstruction	12
2.1. Theories.....	12
2.1.1 Photon absorption.....	12
2.1.2 Phonon generation.....	14
2.2. Photoacoustic Implementations.....	16
2.2.1 Photoacoustic microscopy	16
2.2.2 Photoacoustic computed tomography	18
2.2.3 Photoacoustic endoscopy.....	19
2.2.4 All-optical photoacoustic system	19
2.3. Photoacoustic Image Reconstruction.....	20
2.3.1 Time domain back projection reconstruction algorithm.....	20
2.3.2 Frequency domain synthetic aperture focusing algorithm	22
2.3.3 Frequency domain Stolt reconstruction algorithm.....	23
2.3.4 Time reversal reconstruction algorithm.....	24
2.3.5 GPU-accelerated 2D synthetic aperture focusing algorithm	25
2.3.5.1 2D-SAFT algorithm	26
2.3.5.2 Implementation of 2D-SAFT on GPU	31
2.3.5.3 Experimental demonstration of GPU-accelerated 2D-SAFT.....	33

2.3.5.4 Conclusion.....	39
Chapter 3. An All-in-one Handheld Photoacoustic 3D Imager.....	41
3.1. Introduction	41
3.2. Handheld Photoacoustic System Design.....	45
3.2.1 Optical module design	46
3.2.2 Acoustic module design.....	47
3.2.3 Photoacoustic matching layer design	48
3.2.4 Data acquisition and image display.....	50
3.3. Phase Shift Migration Method for Fast Photoacoustic Reconstruction	50
3.4. Imaging Performance Characterization of the Handheld Photoacoustic Imager	56
3.4.1 Handheld photoacoustics guided needle biopsy	56
3.4.2 Handheld photoacoustics guided thermal therapy and temperature monitoring	60
3.5. Discussion and Conclusion	63
Chapter 4. A Miniaturized Handheld Photoacoustic 3D Imager.....	66
4.1. Introduction	67
4.2. Handheld Photoacoustic System Design.....	68
4.2.1 Handheld probe design	68
4.2.2 Photoacoustic sensitivity distribution.....	71
4.2.3 Data acquisition and image reconstruction.....	74
4.3. Imaging Performance Characterization of the Handheld Photoacoustic Imager	75
4.3.1 Resolution characterization of the handheld photoacoustic imager.....	75
4.3.2 Handheld photoacoustics guided <i>in-vivo</i> needle biopsy.....	77
4.3.3 Handheld photoacoustic imaging of human arm vasculature.....	81
4.4. Conclusion.....	83
Chapter 5. A Portable Photoacoustic Temperature Sensing System	85
5.1. Introduction	85
5.2. Theory of Photoacoustic Temperature Measurement	87
5.3. System Design	88
5.3.1 Optical module design	89
5.3.2 Acoustic module design.....	90
5.3.3 Laser driver circuit design	90
5.3.4 Data acquisition and temperature readout	91
5.4. Results and Discussion.....	92

5.4.1 Phantom experiment.....	92
5.4.2 <i>In-vivo</i> experiment.....	93
5.4.3 Performance discussion	93
5.5. Conclusion.....	95
Chapter 6. A Wearable Photoacoustic 3D Imager	96
6.1. Introduction	97
6.2. System Design and Development.....	99
6.2.1 System overview	99
6.2.2 Optical module design.....	100
6.2.3 Acoustic module design.....	104
6.3. Imaging Performance Characterization of the Wearable Photoacoustic Imager.....	108
6.3.1 Resolution characterization of the wearable photoacoustic imager	108
6.3.2 Wearable imaging of human arm vasculature and SO ₂ monitoring.....	110
6.3.3 Handheld scanning of human breast phantom and melanoma detection	112
6.4. Conclusion.....	115
Chapter 7. Conclusion and Future Work.....	117
7.2. Conclusion.....	117
7.2. Future Work	118
Author's Publication	120
Bibliography	122

Summary

Medical imaging is a “magic” technique of creating a visual representation of the internal human body (hidden by the skin and bones) for clinical analysis and medical diagnosis. Photoacoustic imaging, a new-emerging medical imaging modality, is a powerful tool to perform five-dimensional imaging in the physiological environment by “listening to the sound of light”.

Though the photoacoustic technique witnessed skyrocketing growth since its emergence, however, it has not been effectively applied in clinics. Though the photoacoustic technique takes advantage of the merits of both optical and ultrasound methods, it also integrates the system complexity of both sides, inevitable contributing to bulky and complicated system implementations. For the practical applications of the photoacoustic technique, handheld imaging was proposed and has been widely studied in the recent several years. However, the current-available handheld imaging systems all suffer various limitations, including trivial acoustic coupling, relatively large footprint, inhomogeneous photoacoustic sensitivity, low efficiency of photoacoustic field overlap, etc.

To solve these problems, this thesis is mainly devoted to design and develop handheld photoacoustic imagers towards the clinical translation of the photoacoustic technique. In the light of interdisciplinary nature of the photoacoustic technique, the development of handheld photoacoustic 3D imagers requires effort in various aspects, including optical illumination design, acoustic detection design, back-end electronics design, imaging reconstruction algorithm development, and probe mechanical design. This Ph.D. thesis will comprehensively investigate the handheld photoacoustics in these above-mentioned aspects and present a set of developed handheld photoacoustic

systems, including an all-in-one handheld photoacoustic 3D imager, a miniaturized handheld photoacoustic 3D imager, a portable photoacoustic sensing system, and a wearable photoacoustic 3D imager, in the sequence of step by step optimization. Particularly, with the aim of expanding the real-time capability of 3D handheld photoacoustic imaging, a GPU accelerated two-dimensional synthetic aperture focusing algorithm and a layered phase shift migration algorithm are further developed.

In translating photoacoustic imaging from the conventional benchtop platform to a portable or even a wearable device, the proposed novel coaxial photoacoustic design and several developed handheld imagers are demonstrated to effectively miniaturize the imaging probe, reduce the system complexity, enhancing the usability, and may contribute more practical solutions to clinical applications of the photoacoustic technique. Some concepts and special designs may also inspire some interesting ideas inside or beyond the field of medical imaging.

List of figures

Figure 1.1 State-of-the-art handheld photoacoustic imaging probes. PACT: photoacoustic computational tomography; PAM: photoacoustic microscopy.	6
Figure 2.1 Major configurations of photoacoustic imaging. AR-PAM: acoustic resolution photoacoustic microscopy; OR-PAM: acoustic resolution photoacoustic microscopy; PACT: photoacoustic computational tomography; PAE: photoacoustic endoscopy; AOPAI: all-optical photoacoustic imaging.	16
Figure 2.2 Simulation results using different photoacoustic reconstruction algorithms.	22
Figure 2.3 Schematic of the 2D-SAFT reconstruction.	26
Figure 2.4 (a) Geometric modeling of the 2D synthetic aperture algorithm. (b) 2D Fourier spectrum of the aperture function in different SAFT methods.	30
Figure 2.5 (a) Data flow between the GPU and CPU. (b) Simplified code of the 2D-SAFT OpenCL kernel.	32
Figure 2.6 Simulated imaging reconstruction results with various SAFT methods. Point spread function (PSF) analysis is performed at three different positions ($y = -2.5$ mm, 0 mm, 2.5 mm).	33
Figure 2.7 Phantom imaging results with various SAFT methods.	36
Figure 2.8 Time consumption of the 2D-SAFT implemented in CPU and GPU.	38
Figure 3.1 (a-e) State-of-the-art 3D photoacoustic imaging systems. (f) Developed handheld photoacoustic 3D imager. PA: photoacoustic; DAQ: data acquisition system.	42
Figure 3.2 (a) Schematic of the handheld photoacoustic 3D imager with (b) a compact diode laser and (c) a 2D matrix array. (d) Photograph of the developed handheld photoacoustic 3D imager.	45
Figure 3.3 (a) Geometry of the handheld 3D imager. (b) Monto Carlo optical simulation results. (c) k -wave acoustic simulation results. (d) Resultant photoacoustic sensitivity pattern.	48
Figure 3.4 Flowchart of the phase shift migration (PSM) method for photoacoustic reconstruction.	52
Figure 3.5 3D photoacoustics guided needle biopsy with a handheld operation.	57
Figure 3.6 Characterization of imaging resolution for the developed 3D imager. (a) Volume rendered image; (b-d) 2D projected images along the (b) y direction, (c) x direction, and (d) z direction. (e) FWHM analysis.	59
Figure 3.7 Handheld photoacoustics guided thermal therapy and temperature monitoring. (a-d) 3D photoacoustic imaging with handheld operation. (e-k) 3D photoacoustic images encoded with temperature elevation. (l) Tendency of the temperature variation.	61
Figure 3.8 Estimation of system stability for handheld photoacoustic 3D imager.	64
Figure 4.1 (a) Photograph of the developed miniaturized handheld photoacoustic 3D imager. (b) Schematic drawing of the handheld probe.	68
Figure 4.2 (a) Schematic diagram of the light propagation within the handheld probe. (b) Geometric arrangement of the central-holed 2D matrix array.	69
Figure 4.3 (a) Simulated optical fluence map in the x - z plane. (b) Schematic of the photoacoustic overlap. (c) Simulated acoustic sensitivity distribution in the x - z plane. (d) Simulated optical fluence map in the x - y plane. (e) Simulated photoacoustic sensitivity distribution. (f) Simulated acoustic sensitivity distribution in the x - y plane.	71
Figure 4.4 (a) Photograph of the whole portable photoacoustic system. (b) Acoustic reconstructive environment.	74
Figure 4.5 Imaging resolution characterization. (a) Volume rendered photoacoustic images of two hairs. (b, d, f) 2D maximum amplitude projections (MAP). (c, e, g) Line spread function (LSF) analysis.	76
Figure 4.6 Demonstration of handheld volumetric imaging during <i>in-vivo</i> needle biopsy. (a) Photograph of the rat's abdomen, from which the photoacoustic images are captured. (b) Schematic of the handheld operations during photoacoustics guided needle biopsy. (c) An	

untruncated photoacoustic image in 3D space. (d-e) Selected snapshots of photoacoustic video at different time.	78
Figure 4.7 (a) Off-line reconstructed synthesized image using three groups of data. (b) Schematic of the synthesized reconstruction. (c-e) 2D maximum amplitude projection (MAP) images.	80
Figure 4.8 Demonstration of 3D handheld photoacoustic imaging of human arm vasculature. (a) Diagram of the vasculature in human arm. (b-e) volumetric images of the arm vasculature (including the cephalic vein, accessory cephalic vein, and median cephalic vein).	82
Figure 5.1 Schematic of the proposed photoacoustic sensing device for blood temperature measurement. (a) Main body. (b) Sensor head. (c) Measurement timing. (d) Photograph of wearable device.	89
Figure 5.2 Circuit diagram of the laser diode driver.	91
Figure 5.3 Temperature measurement on target phantom with linear fitting. (a) Temperature calibration results. (b) Temperature measurement results.	92
Figure 5.4 Temperature measurement on the rat's tail. (a) Photography of the sensing implementation. (b) Calibration results. (c) Measurement results.	94
Figure 6.1 (a) Photograph of the wearable photoacoustic 3D imager and its potential applications. (b) Exploded view of the 3D imager. (c) Schematic diagram of light propagation within the 3D imager. (d) Schematic diagram of ultrasonic propagation within the 3D imager.	99
Figure 6.2 Photograph of the whole photoacoustic imaging system.	100
Figure 6.3 (a) Circuit diagram of the laser driver. (b-c) Photograph and micrograph of the laser driver board.	102
Figure 6.4 Block diagram of the whole miniaturized photoacoustic imaging system, including the (a) optical assembly, (b) acoustic assembly, and (c) signal processing and image reconstruction chains.	105
Figure 6.5 (a) Spectrums of the raw photoacoustic signals. (b) cross correlation (CCR) results of the raw photoacoustic signals. (c) Reconstructed images of the point testing target. (d) Lateral resolution analysis. (e) Depth resolution analysis.	108
Figure 6.6 Wearable photoacoustic imaging of arm vasculature with (b) 450 nm laser irradiation, (c) 638 nm laser irradiation, and (d) 808 nm laser irradiation. (e) Arm vasculature distribution within the imaging field. (f) Contour 3D image of the superficial cephalic vein (SO ₂ level: 35 %). (g) Contour 3D image of the radial artery (SO ₂ level: 72 %). (f) Photoacoustically measured SO ₂ level in artery and vein.	111
Figure 6.7 Photograph of the human breast phantom. (b-f) Several snapshots of the photoacoustic video when scanning the melanin masses on a human breast phantom. (g) Synthetic photoacoustic image of six melanin masses.	114

List of tables

Table 2.1 Performance comparison among different photoacoustic reconstruction methods.	25
Table 2.2 Comparison of the lateral resolution and imaging SNR with various SAFT methods.	34
Table 6.1 Detailed specification of the laser diodes.	101

Chapter 1. Introduction

In section 1.1, an overview of the photoacoustic technique (especially biomedical photoacoustic imaging) is first introduced. Based on the state-of-the-art development of the photoacoustic technique, section 1.2 gives the motivation and objectives of my research. In section 1.3, the major contributions of this thesis are presented, ranging from system developments, probe designs, reconstruction algorithm developments, to the biomedical applications. Finally, in section 1.4, an outline of the whole thesis is provided.

1.1. Overview of the Photoacoustic Technique

The discovery of the photoacoustic effect can be traced back to 1880 when Alexander Graham Bell observed the sound generation from a selenium cell followed by the absorption of modulated sunlight [1]. Though this exciting phenomenon attracted fervent research interests in a short term, the study of the photoacoustic effect slightly stagnated in the later several decades, since quantitative experiments were difficult to perform [2]. In 1938, Mark Veingerov proposed a photoacoustic gas analyser to detect CO₂ concentration in N₂ environment [3]. Motivated by this, the photoacoustic technique had been applied in wide chemical applications, such as measurement of energy transfer rate and vibrational relaxation rate [4]. One milestone in the development of the photoacoustic technique is the invention of laser technology in the 1960s. The high peak power, high directivity, and high stability achievable with laser technology make it possible for the photoacoustic technique to be used in industries (*e.g.* solids spectroscopy [5], non-destructive testing [6]).

The application of photoacoustic effect in the biomedical field was first investigated in 1964 [7]. Amar *et al.* demonstrated the generation of transient ultrasound pressure from the retina, upon a 50 mJ laser pulse irradiation into the eye of a living rabbit. Followed by this study, a hand of scientists reported their studies about applying the photoacoustic technique to biological components microanalysis [8], tissue properties determination [9], turbid tissue visualization [10], *etc.* With the development of biomedical photoacoustic imaging, advocated by several groups (*e.g.* Robert A. Kruger [11],[12], André Dekker [13], Lihong V. Wang [14], Paul C. Beard [15]), another revival of the photoacoustic technique took place at the end of the 20th century. These works were considered to set the keynote for the development of the biomedical photoacoustic technique, in which a high-energy pulsed laser is normally employed for optical excitation and a high-frequency ultrasound transducer array or a scanning large-NA focused ultrasound transducer is employed for acoustic detection [16]. Thereafter, more and more researchers realized the superiority of the photoacoustic technique over its primordial single-wave imaging modalities (*i.e.* optical imaging and ultrasound imaging). For example, in optics-based imaging modalities, such as optical coherence tomography [17] and fluorescence imaging [18], though images with excellent resolutions and high specificities can be obtained in some superficial applications, the effective imaging depth is only about a few sub-micrometers (ballistic regime). On the other hand, pure ultrasonics-based imaging modalities (ultrasonography) can provide high spatial resolutions in the optical quasi-diffusive and diffusive regime, since the scattering of ultrasound wave in biological tissue is much lower than that of light (about 2 ~ 3 orders of magnitude). However, ultrasound imaging shows relatively weak contrast and poor specificity, due to the small difference of the mechanical properties (acoustic mismatch) between different

soft tissues, unless in some special imaging scenarios (*e.g.* fetus in the uterus). Photoacoustic imaging can magically take advantage of the rich contrast/specificity of optical imaging and the high spatial resolutions of ultrasound imaging, while overcome the limitation of both methods. Besides, photoacoustic imaging is speckle-free and immune from speckle artifacts, which are unattainable in both optical coherence tomography and ultrasound imaging [19]. With all these advantages, on the application of the photoacoustic technique into the biomedical imaging field, the development of the photoacoustic technique kicked into high gear.

From the beginning of 21 century to the present, profiting from the fast-developing laser technology and ultrasonic technology, the photoacoustic technique witnessed explosive growth in terms of mechanism explorations (*e.g.* Grueneisen relaxation photoacoustics [18], nonlinear photoacoustics [21], two-photon second-harmonic photoacoustics [22], contrast agent based photoacoustics [23], photoacoustic cavitation [24], stimulated Raman photoacoustics [25], Doppler photoacoustics [26], continuous wave (CW) modulated photoacoustics [27], super-resolution photoacoustics [28], functional photoacoustics [29], multi-scale photoacoustic [30], *etc.*); system developments (*e.g.* acoustic resolution photoacoustic microscopy [31], optical resolution photoacoustic microscopy [32], linear array based photoacoustic tomography [33], curved array based photoacoustic tomography [34], photoacoustic endoscopy [35]), all-optical photoacoustic imaging [36], reconstruction algorithm developments (*e.g.* back projection algorithm [37], time domain synthetic aperture focusing algorithm [38], frequency domain synthetic aperture focusing algorithm [39], frequency domain Stolt migration algorithm [40], time reversal algorithm [41], model based algorithm [42], Radon transform algorithm [43], *etc.*); and pre-clinical applications (*e.g.* photoacoustic elastography [44], photoacoustic

Doppler flowmetry [45], photoacoustic thermometry [46], photoacoustic ophthalmoscopy [47], photoacoustic blood cytometry [48], hemoglobin oxygen saturation level measurement [49], glucose level measurement [50], blood PH measurement [51], early cancer detection [52], fingerprint identification [53], *etc.*). All these achievements have greatly promoted the prosperity of the photoacoustic technique, and simultaneously drive the development of other multi-wave imaging modality, such as thermoacoustic imaging [54], magnetically modulated thermoacoustic imaging [55], X-ray induced thermoacoustic imaging [56], magnetoacoustic imaging [57], magnetomotive ultrasound imaging [58], magnetomotive photoacoustic imaging [59], *etc.*

Up till now, the photoacoustic technique has evolved from a one-dimensional (1D) *Photophone* [1] to a five-dimensional (5D) imaging modality [60]. Essentially, photoacoustic imaging is *per se* a three-dimensional (3D) imaging method, in which the first two spatial dimension is provided by the acoustic detection aperture (either in the way of mechanical translation [31] or straightforwardly using a matrix ultrasound transducer array [61]), while the third dimension is ensconced in the time-of-flight information of photoacoustic wave and will be converted to the real spatial dimension after projective reconstruction. The real-time imaging capability [62], benefiting by the implementation of parallel acoustic signal detection, contributes to the fourth dimension of photoacoustic imaging. Such a temporal dimension endows photoacoustic imaging with the capability of monitoring dynamic phenomena such as targeted drug delivery, temperature variation, contrast agent uptake, metabolism, *etc.* Lastly, the implementation of the fifth dimension—the spectral dimension is realized by incorporating the fast wavelength-tuning OPO laser into the four-dimensional photoacoustic (4D) imaging system. Accordingly, by facilitating the multi-wavelength

3D photoacoustic imaging in real-time, a 5D photoacoustic imager with three spatial dimensions, one temporal dimension, and one spectral dimension is achievable and named as fast multispectral optoacoustic tomography (MSOT) [63]. These breathtaking achievements provide new insights into the photoacoustic technique and open new possibilities in medical imaging.

1.2. Motivation and Objectives

In spite of the impressive progress of the photoacoustic technique in various aspects, there is still a great gap between the requirement for clinical applications and the state-of-the-art photoacoustic technique. One major limitation that hinders its way for clinical translation is the complexity of the photoacoustic implementation. Though the photoacoustic technique takes advantage of the merits of both optical imaging and ultrasound imaging, it also integrates the system complexity from both sides. Optically, to pursue high-sensitivity photoacoustic generation and consequently high-contrast image formation, a high-power laser source is generally required. When it comes to the addition of the fifth dimension—the spectral dimension, an optical parametric oscillator (OPO) system is indispensable. Inevitably, this leads to a bulky system configuration, not to mention the extra size expansion brought by the affiliated cooling system and stability control system (*e.g.* vibration-isolated optical table) [32]. Moreover, the high cost and required careful maintenance of the laser system pose a challenging obstacle for the clinical application of the photoacoustic technique. Acoustically, to pursue respectable imaging performances in the temporal dimension, a fast-scanning motorized stage [64] or a large-aperture ultrasound transducer array [65] is necessary. However, such induced large-scale acoustic implementation makes it particularly challenging to miniaturize the photoacoustic implementation.

Additionally, the acoustic coupling between photoacoustic imaging probe and the imaging target is still a nontrivial task. Unlike the direct-contact imaging mode (with ultrasonic couplant) in ultrasonography, additional water coupling in the form of water tank [31], water packet [66], or water cage [67] is still necessary for photoacoustic imaging.

Figure 1.1 State-of-the-art handheld photoacoustic imaging probes. PACT: photoacoustic computational tomography; PAM: photoacoustic microscopy.

With the aim of miniaturizing the photoacoustic imaging platform, reducing the system complexity, and improving the imaging flexibility, handheld photoacoustic imaging emerged accordingly. Differing from the traditional benchtop imaging systems, the handheld photoacoustic imager typically employs a free-moving imaging probe, whose imaging field of view (FOV) can be easily manipulated. Modified on the conventional B-mode ultrasonographic platform, a two-dimensional (2D) handheld photoacoustic imaging system using a linear array [Figure 1.1(a)] was first proposed by Martin Frenz [68]. Subsequently, similar implementations with some minor optimization are developed [69]-[72]. Alternatively, the linear array can be replaced by a curved array ($120 \times 40 \text{ mm}^2$). Such a curved array based handheld

tomographic system (called 2D-MSOT [73]) can increase the sensitivity at the center of the imaging field while at the cost of reducing the FOV, as depicted in Figure 1.1(b). In these designs, optical illumination is provided on the lateral sides of the linear array, except in Ref. [74][75], in which a coaxial photoacoustic implementation is designed with the use of acoustic reflective mirrors. Though these two kinds of handheld implementations enable fast motion-insensitive imaging, only 2D tomographic images in the ultrasonic plane can be obtained. Mechanical scanning of the handheld probe can form the volumetric images, nevertheless, leading to a compromised frame rate and anisotropic lateral resolutions [76]. To achieve handheld imaging in 3D space, handheld photoacoustic imaging using a hemispherical matrix array ($\varnothing$: 80 mm, height: 200 mm) was further investigated and developed by several groups [63],[66],[77]-[80], as shown in Figure 1.1(c). Empirically, the active acoustic visualization region is limited in a small sphere with a radius that is one-fourth of the radius of the spherical transducer array [15]. Therefore, there is always a contradiction between the FOV and the probe size when the coverage angle is fixed. In addition, to fill the cavity beneath the spherical aperture, a membrane-sealed water chamber was employed for necessary acoustic coupling. Such a susceptible coupling design needs careful maintenance and periodical replacement (*e.g.* heavy water and sterile condition) and may not be suitable for rough handling in handheld imaging. 3D handheld imaging is also available by employing a 2D matrix array and two off-axis laser fiber bundles ($> 100 \times 100 \text{ mm}^2$) [81], as shown in Figure 1.1(d). Similar to its simplified 2D version [70], most of the optical energy is deposited outside the region of interest (ROI), which is undesirable in developing a miniaturized photoacoustic imager that requires high optical efficiency. Besides, homogeneity of optical fluency cannot be guaranteed if no optical compensator (gel pad in Ref [82]) is supplemented. Except

for photoacoustic tomographic systems, handheld design was also implemented on photoacoustic microscopy platforms [83],[84]. By integrating a 2-axis MEMS scanner into the photoacoustic probe [Figure 1.1(e)], handheld imaging with a high resolution ($< 30 \mu\text{m}$) is available. However, this handheld design is limited in the frame rate (20 seconds per frame) and FOV (several cubic millimeters). Taken together, a fundamental limitation common to most handheld platform is the relatively large footprint and weight, which greatly influences the imaging flexibility and usability for handheld operations. Another limitation is the relatively low efficiency of photoacoustic field overlap (the overlap between the optical illumination pattern and the acoustic detection sensitivity), which increases the burden of the photoacoustic probe and indirectly contributes to a large footprint. Additionally, as mentioned before, most of the handheld systems [Figure 1.1(b-e)] require the assistant from the water medium for adequate acoustic coupling. Therefore, based on these limitations, the objectives of this thesis are stated as follows.

- ✚ The primary objective of this thesis is to design and develop a handheld photoacoustic 3D imager and demonstrate its applications in theranostics.
- ✚ To develop a water-free handheld imaging probe that supports relatively rough handheld operations and does not need captious maintenance.
- ✚ To miniaturize the 3D imager to be a lightweight and small-footprint handheld probe that supports convenient and flexible handheld operations.
- ✚ To investigate a more efficient photoacoustic solution with high utilization of optical energy, high sensitivity of acoustic detection, and high efficiency of photoacoustic overlap.
- ✚ To enhance the homogeneity of photoacoustic sensitivity pattern in the

imaging FOV and make it possible for 3D handheld photoacoustic imaging to be applied in some quantitative applications, such as thermal/temperature mapping and hemoglobin oxygen saturation level monitoring.

1.3. Major Contributions

Corresponding to the pre-set objectives, in the past few years, we have actively investigated the optimal handheld solutions for 3D photoacoustic imaging. This thesis, as a summary of my contribution to the handheld photoacoustics, is mainly devoted to designing handheld photoacoustic 3D imagers/sensors and developing fast reconstruction algorithms for 5D implementation of the photoacoustic technique. Therefore, the major contributions of this thesis can be reflected in two aspects:

System development: We first proposed and developed an all-in-one handheld photoacoustic 3D imager, in which all the optical units, the acoustic units, and the photoacoustic matching unit are integrated into a single compact handheld probe (*i.e.* all-in-one). Particularly, the introduction of the photoacoustic matching unit makes the handheld 3D imager become a completely water-free solution. Benefiting by the tight coaxial design, high-efficiency photoacoustic detection with homogeneous sensitivity is achieved. Later, to reduce the weight and footprint of the handheld imaging probe, we further developed a miniaturized handheld photoacoustic 3D imager, as the second generation of our handheld imaging system. Based on our work of photoacoustic temperature sensor, we developed a wearable photoacoustic 3D imager (as the third generation) with coherent frequency domain photoacoustics, to expand the imaging dimension towards the spectral domain (the fifth dimension). At this point, a miniaturized,

water-free, high-sensitivity, and high-homogeneity solution for 3D handheld photoacoustic imaging is proposed and demonstrated.

Algorithm development: In photoacoustic imaging with planar detection geometry, to accelerate the back projection in 3D space, a GPU-accelerated two-dimensional synthetic aperture focusing technique (2D-SAFT) is developed and implemented with OpenCL framework. In handheld photoacoustics, to cater to the stratified structure in the designed handheld photoacoustic 3D imager, fast frequency domain phase shift migration (PSM) method is developed. Both fast realizations of photoacoustic imaging reconstruction are devoted to promoting the handheld photoacoustic technique in the temporal dimension.

1.4. Organization of the Thesis

After a brief overview of the photoacoustic technique in the first chapter, this thesis sets out with the fundamental mechanism of the photoacoustic generation in section 2.1. In section 2.2, several mainstream implementations of the photoacoustic technique are introduced. In section 2.3, several major image reconstruction algorithms are summarized. Particularly, our proposed fast 2D-SAFT algorithm is described in detail in this section.

In the third chapter of the thesis, an all-in-one handheld photoacoustic 3D imager is proposed. Following a brief introduction of the state-of-the-art 3D imaging technology (section 3.1), the detailed design of the handheld probe (including optical design, acoustic design, and photoacoustic matching design) is described in section 3.2. Section 3.3 proposes a novel reconstruction algorithm for fast layered photoacoustic reconstruction, which is exclusively designed for the real-time

handheld photoacoustic imaging. Imaging results implemented by this handheld 3D imager are provided in section 3.4.

In the fourth chapter, a miniaturized handheld photoacoustic 3D imager, as the second generation of our handheld imaging system, is presented. With more compact optical design and improved photoacoustic matching design, a highly compact handheld probe with portable backend electronics is developed (section 4.2). *In-vivo* demonstrations on “soft” tissue (rat’s abdomen) and “hard” tissue (human arm) are provided in section 4.3.

In the fifth chapter, before the investigation of the wearable handheld 3D imager using the CW laser, a preliminary work—development of a portable photoacoustic temperature sensing device is presented. The theory of photoacoustic thermometry, system development, and experimental demonstration results are provided in section 5.2, section 5.3, and section 5.4, respectively.

Chapter 6 presents an integrated wearable photoacoustic 3D imager, as the third generation of our handheld photoacoustic imager. In comparison with the pulsed laser based first two generations of the photoacoustic 3D imagers, CW laser based photoacoustic imager achieves further system miniaturization without the degradation of imaging performances. System development and probe design are discussed in detail in section 6.2. Characterization of imaging performances is provided in section 6.3.

Finally, chapter 7 is bringing together the conclusions of the thesis and prospects for future research are provided.

Chapter 2. Photoacoustic Imaging: Theories, Implementations and Reconstruction

2.1. Theories

The fundamental principles of the photoacoustic effect can be described in brief as, photoabsorbers in biological tissue, such as endogenous biological matter and exogenous contrast agent, absorb optical energy, giving rise to localized thermal energy accumulation, transient temperature elevation, and subsequent thermoelastic vibration of the photoabsorbers or the surrounding medium, which propagates out in the form of ultrasound wave.

2.1.1 Photon absorption

Interactions between light and biological tissue have been widely studied, such as Rayleigh scattering, Raman scattering, absorption, polarization, fluorescence, *etc.* Among all the above photon behaviors, the most important interactions that affect the imaging performances of the photoacoustic technique are the optical scattering and optical absorption. Optical absorption determines the origin of photoacoustic generation, imaging specificity, and imaging contrast, whereas optical scattering deteriorates the imaging resolution at depth, especially for optical resolution photoacoustic imaging modalities [85].

In human biological tissues, light transfer is dominated by scattering and diffusion. Beyond the transport mean free path (~ 0.099 mm [19]), photons enter the diffusive regime and undergo significant scattering, making the focusing based optical sensing techniques ineffective. Therefore, typical optical techniques with diffused light can only achieve a resolution of about 1 cm [86]. On the other hand, in the medium

containing strong photoabsorbers (*e.g.* hemoglobin and cytochrome), although scattering broadens and attenuates light greatly, the generated photoacoustic wave provides better resolution than the optical wave, because the ultrasonic scattering is two to three orders of magnitude weaker than the optical scattering [87].

The most commonly photoabsorbers for photoacoustic imaging can be classified into two categories based on their primary absorbing wavelengths: (1) in the visible regions (400 ~ 700 nm), the primary absorbers include hemoglobin [88], cytochrome [89], melanin [90], DNA/RNA [91], myoglobin [92]; (2) in the near-infrared region (700 ~ 1400 nm), lipid [93], glucose [94] are also strong absorbers for photoacoustic emission. Among these, hemoglobin is most commonly used as the photoacoustic label, which gives rise to a high absorption contrast (> 100) between blood vessels and the background tissue. Besides, the difference of absorption spectrum between oxygenated and deoxygenated hemoglobin makes the photoacoustic technique intrinsically suited for spectroscopic detection, providing the fifth dimension of photoacoustic imaging.

Two types of laser sources can be employed to generate photoacoustic signals: pulsed laser and intensity-modulated continuous wave (CW) laser. Although the CW-photoacoustic method shows wide advantages including the compact system size, low cost, low power consumption, and portability, nanosecond pulsed laser is still preferred to provide a higher signal-to-noise ratio (SNR) and direct detection of the distance of the source through the time-resolved photoacoustic signals. Upon the laser irradiation on the imaging target, the heating function $H(r, t)$, as the source term to induce photoacoustic generation, can be expressed as

$$H(r, t) = \mu(r)\phi(r, t), \quad (2.1)$$

in which $H(r,t)$ is the absorbed energy per unit time and per unit volume, $\phi(r,t)$ is the light fluence, and $\mu(r)$ is the optical absorption coefficient, which describes the photon absorption per unit path length.

2.1.2 Phonon generation

To generate photoacoustic waves efficiently, two conditions, referred to as thermal and stress confinements, must be satisfied. Firstly, the laser pulse used to stimulate the biological tissue should have a pulse width τ smaller than the characteristic thermal relaxation time τ_{th} so that thermal diffusion can be neglected. Such a condition is called the thermal confinement condition. Normally, the time scale for the heat dissipation in biological tissue by thermal conduction is about several milliseconds. In photoacoustics, to generate efficient ultrasound waves in the megahertz (MHz) range, the time duration of the laser pulse is always from several nanoseconds to microseconds, which is much less than the required thermal confinement relaxation time. On the other hand, the laser pulse width should also be smaller than the time for the stress to exit the heated region, which is commonly known as the stress confinement [87]. When this condition is satisfied, high thermoelastic pressure in the tissue can build up rapidly. For example, to achieve a spatial resolution of 100 μm , the acoustic relaxation time is more than several tens of milliseconds. Therefore, the acoustic confinement condition can also be easily satisfied.

Upon the fulfillment of the thermal confinement and stress confinement, thermal diffusion and fractional volume expansion can be negligible. The initial pressure $p_0(r)$ immediately after the laser absorption can be derived as follows:

$$p_0(r) = \frac{\beta c^2}{C} A(r), \quad (2.2)$$

in which β is the thermal coefficient of volume expansion, C is the specific heat capacity of the tissue medium, c is the speed of sound, and $A(r)$ is the optical energy deposition density. Therefore, the initial photoacoustic pressure is directly related to the spatial distribution of heat deposition. Such acoustic transient pressure inside the tissue acts as the initial condition in the general acoustic wave equation:

$$\nabla^2 p(r, t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p(r, t) = -\frac{\beta}{C} \frac{\partial}{\partial t} H(r, t). \quad (2.3)$$

The generated photoacoustic waves propagate through the tissue and are detected by an ultrasonic transducer or transducer array at the tissue boundary. Solved by three-dimensional (3D) Green function method [95], the photoacoustic signal picked up by an ideal point ultrasound transducer can be written as

$$p(r_d, t) = \frac{\beta}{4\pi C} \frac{\partial}{\partial t} \int dr \frac{1}{|r_d - r|} H(r, t - \frac{|r_d - r|}{c}). \quad (2.4)$$

Equation (2.4) tells us that the detected acoustic pressure at the spatial location r_d and time t comes from an acoustic source integrated over a spherical shell centered at r_d with a radius of ct . Such a direct relationship between the generated acoustic pressure and the capabilities of optical absorption permits the structural imaging reconstruction and quantification of various physiological parameters such as the oxygenation of hemoglobin. Besides, in the process of laser heating, the transient temperature elevation is only about several millidegrees Celsius [96], and thus will not change the properties of the biological tissue under study, making the photoacoustic technique suitable for wide biomedical imaging and sensing applications.

2.2. Photoacoustic Implementations

The typical photoacoustic imaging process usually involves optical irradiation, ultrasonic detection, and finally image formation. Based on different types of optical illumination and ultrasonic detection methods, photoacoustic imaging can be implemented in four major configurations—photoacoustic microscopy (PAM), photoacoustic computed tomography (PACT), photoacoustic endoscopy (PAE), and all-optical photoacoustic imaging (AOPAI).

Figure 2.1 Major configurations of photoacoustic imaging. AR-PAM: acoustic resolution photoacoustic microscopy; OR-PAM: optical resolution photoacoustic microscopy; PACT: photoacoustic computational tomography; PAE: photoacoustic endoscopy; AOPAI: all-optical photoacoustic imaging.

2.2.1 Photoacoustic microscopy

PAM typically employs focused optical illumination, focused ultrasound detection, and a linear scanning platform. Like the optical confocal microscopy, a confocal photoacoustic design is implemented to pursue an optimized efficiency of

photoacoustic conversion and imaging sensitivity. Depending on who provides the minimum focal spot, PAM is mainly classified into two categories—acoustic-resolution photoacoustic microscopy (AR-PAM) and optical-resolution photoacoustic microscopy (OR-PAM). If the acoustic focal spot is smaller than the optical focal spot, *i.e.* the imaging resolution is provided by a high numerical aperture (NA) focused ultrasound transducer, such an imaging platform is termed AR-PAM [31]. Since optical focusing only improves the sensitivity of photoacoustic detection while shows little influence on the imaging resolution, tight optical focusing is not necessary [97]. For example, in dark-field AR-PAM as shown in Figure 2.1(a), laser illumination is delivered around the focused ultrasound transducer with the help of an optical condenser, by which a loosely focused optical pattern is overlapped with the tightly focused ultrasound beam.

If the optical focal spot is smaller than the acoustic focal spot, *i.e.* the imaging resolution is optically determined by the beam size at the focal plane, such an imaging platform is termed OR-PAM [32]. Figure 2.1(b) shows an example of the reflection-mode OR-PAM system. Unlike the loose weak optical focusing in AR-PAM, a tight optical focal spot is straightforwardly obtained with the use of a high-NA focusing lens while the generated photoacoustic wave is reflected by an acoustic mirror and further received by a focused ultrasound transducer. Other forms of OR-PAM, such as double-reflection OR-PAM [98], transmission-mode OR-PAM [99], spatially invariant resolution OR-PAM [100], double-illumination OR-PAM [101], were also developed with similar assembly and for different imaging scenarios and applications.

As a rule of thumb, OR-PAM offers a much higher lateral resolution (up to 220 nm [102]), while in AR-PAM, acoustic-diffraction physically limits the lateral resolution to be about several tens of micrometers (*e.g.* 45 μm for a 0.44 NA, 50 MHz

ultrasound transducer [31]). On the other hand, AR-PAM offers a much deeper penetration depth (up to 3 cm [103]), whereas OR-PAM only works in a superficial imaging situation (penetration depth < 1 mm). To take full advantage of the multi-scale imaging capability of PAM, hybrid-mode PAM that enables automatically co-registered high-resolution OR-PAM and deep-penetration AR-PAM were developed [104][105].

2.2.2 Photoacoustic computed tomography

PACT, sharing a great many similarities with X-ray computed tomography, is considered as a more practical photoacoustic solution with better flexibility and less restriction. In PACT, expanded optical irradiation illuminates the entire region of interest (ROI) and generated photoacoustic waves are detected by mechanically scanning a single ultrasound transducer or with an array of ultrasound transducers. Figure 2.1(c) depicts the configuration of the linear array PACT, in which light delivery through two fiber bundles are provided at the lateral sides of an ultrasound linear array [33], as in AR-PAM. Figure 2.1(d) depicts the configuration of the circular array PACT, in which ultrasound detection can be performed using a circular ultrasound array or rotationally scanning a single-element transducer [106]. Alternatively, the scanning single-element transducer can be upgraded to a linear array or a curved array, leading to the volumetric version of PACT—cylindrical array PACT [107] and spherical array PACT [108]. Unlike in PAM that photoacoustic images are straightforwardly obtained after linear scanning in the horizontal direction, image formation in all the above PACT implementations rely on an inverse algorithm to reconstruct the distribution of the photoacoustic sources.

2.2.3 Photoacoustic endoscopy

On the basis of the ultrasonic endoscopic device, photoacoustic endoscopy was developed with the aim of better visualization of the pathologic conditions in some internal organs, such as esophagus, urethra, and colon. Figure 2.1(e) depicts the schematic of a typical PAE device [109], which compromises a center-holed focused ultrasound transducer, a multimode optical fiber that passes through the ultrasound transducer, and a mirror for reflecting the laser light into the biological tissue and reflecting the generated photoacoustic wave to the ultrasound transducer. By magnetically rotating the endoscopic probe and acquiring the time-resolved acoustic signal at each angular step, 2D sectorial photoacoustic images can be obtained. Further volumetric visualization of the internal structure can be realized by mechanical pullback of the endoscopic probe and simultaneously data acquisition [35].

2.2.4 All-optical photoacoustic system

Unlike the typical photoacoustic imaging systems that employ piezoelectric ultrasound transducers (*e.g.* PZT, piezoelectric composite, and PVDF), AOPAI uses the purely optical method to acquire the generated photoacoustic wave [110]. With the advantages of ease of miniaturization [111], non-contact imaging capability [112], and ultrabroad bandwidth [36], AOPAI has its unique place among all the photoacoustic imaging implementations. A representative of AOPAI is illustrated in Figure 2.1(f), which contains two different lasers—an excitation laser for photoacoustic wave generation and an interrogation laser for photoacoustic signal acquisition [113]. Working in the AR-PAM mode, volume rendered photoacoustic image is formed by scanning the focused interrogation laser in the x - y plane using a galvanometer scanner. Though other forms of AOPAI, such as all-optical OR-PAM

[112] and all-optical PAE [114], were subsequently emerged, the key design is still based on the optical based ultrasound detection method.

2.3. Photoacoustic Image Reconstruction

The key to success in handheld photoacoustic imaging is the development of the appropriate reconstruction algorithm. As before, various reconstruction algorithms with respect to different detection geometries (*e.g.* planar, spherical, and cylindrical), different reconstruction scenarios (*e.g.* acoustically homogeneous, acoustically inhomogeneous, acoustically stratified), and different performance requirements (*e.g.* high imaging resolutions, short time consumption, low memory cost) have been extensively investigated. A short review section in this thesis can only cover a limited amount of existing methods for photoacoustic reconstruction. Given the major topic of this thesis is about handheld photoacoustic imaging and the key design of our developed handheld photoacoustic imager is a planar matrix array, for similarity, only photoacoustic reconstruction algorithms with planar detection configuration are discussed in this section. More comprehensive introductions and demonstrations of photoacoustic imaging using spherical, cylindrical, and arbitrary detection configurations can be found in Ref. [115]-[118].

2.3.1 Time domain back projection reconstruction algorithm

In section 2.2.2, Equation (2.4) gives a general form of the transient acoustic pressure, which provides a direct relationship between the received photoacoustic pressure and the optical absorption distribution. Considering the quasi-static condition and the nanosecond pulsed laser irradiation, the heating function can be approximately separated to a spatial term $A(r)$ and a delta temporal term $\delta(t)$, as

$$p(r_d, t) = \frac{\beta}{4\pi C} \frac{\partial}{\partial t} \int dr \frac{1}{|r_d - r|} A(r) \delta(r, t - \frac{|r_d - r|}{c}). \quad (2.5)$$

Using Equation (2.2), the final form of the time domain back projection algorithm for an arbitrary detection geometric can be expressed as

$$p(r_d, t) = \frac{1}{4\pi c^2} \frac{\partial}{\partial t} \left[\frac{1}{ct} \int dr p_0(r) \delta(r, t - \frac{|r_d - r|}{c}) \right]. \quad (2.6)$$

When the acoustic detectors are arranged in a 1D planar geometry (a linear ultrasound transducer array place in the x direction), the uniform projection algorithm is demoted to a 2D time domain synthetic aperture focusing algorithm, as [38]

$$p_0(x, z) = \sum_{m=1}^N p(m, \frac{\sqrt{(x-x_m)^2 + z^2}}{c}), \quad (2.7)$$

where $p_0(x, z)$ denotes the reconstructed acoustic pressure at an arbitrary position (x, z) in the imaging plane (x - z plane), $P(m, t)$ is the time-varying raw data received by the m 'th transducer element placed at $(x_m, z=0)$, $\frac{\sqrt{(x-x_m)^2 + z^2}}{c}$ is the acoustic time of flight from the synthetic focus to the m 'th transducer.

For a more straightforward demo of the reconstruction effect of the back projection algorithm, a numerical simulation is performed in the k -wave framework [119]. In the simulation, three ideal point photoabsorbers (diameter: 150 μm) are placed at different depths (9.6 mm, 22.4 mm, and 35.2 mm). A linear ultrasound array (element width: 150 μm , pitch: 300 μm , number of elements: 100, center frequency: 5 MHz, frequency bandwidth: 60 %) is implemented in the x direction at the zero depth ($z=0$) to receive the photoacoustic response in a 2D tomographic plane. Figure 2.2(a) shows the simulated results, in which Gaussian distributed random noise is further

added into the raw data to result in an SNR of 7.4 dB. After the time domain back projection reconstruction, imaging SNR is improved to be about 38.7 dB [Figure 2.2(b)].

Figure 2.2 Simulation results using different photoacoustic reconstruction algorithms.

2.3.2 Frequency domain synthetic aperture focusing algorithm

The time domain back projection is mathematically straightforward and easy to implement in practical imaging. However, it suffers restricted computational efficiency and requires relatively long processing time. Alternatively, a frequency domain synthetic aperture focusing algorithm (F-SAFT) can be implemented in the planar detection geometry [39].

In F-SAFT, the recorded pressure waves $p(x, z=0, t)$ are firstly projected to the wavenumber-frequency domain with the 2D Fourier transform, as

$$p(x, z=0, t) = \iint P(k_x, z=0, \omega) e^{ik_x x} e^{-i\omega t} dk_x d\omega, \quad (2.8)$$

where k_x represents the wavenumber in the x direction, and ω represents the angular frequency. In the following, the photoacoustic field at $z=0$ in the wavenumber-frequency domain can be extrapolated to any other depths z with the use of a phase shift “propagator”, as

$$P(k_x, z, \omega) = p(k_x, 0, \omega)e^{\pm ik_z z}, \quad (2.9)$$

where k_z is the wavenumber in the z direction and satisfies the relationship:

$(\omega/c)^2 = k_x^2 + k_z^2$. Finally, the initial acoustic pressure field $p_0(x, z)$ can be reconstructed by

$$p_0(x, z) = \iint P(k_x, z=0, \omega)e^{ik_x x} dk_x d\omega \quad (2.10)$$

This integral can be executed by first integrating the extrapolated acoustic field over ω , followed by the inverse Fourier transform over k_x . Figure 2.2(c) shows the F-SAFT reconstructed photoacoustic imaging results, in which the imaging SNR is estimated to be about 42.1 dB.

2.3.3 Frequency domain Stolt reconstruction algorithm

In the frequency domain, another efficient reconstruction method is the Stolt f - k migration algorithm [120]. Similar to the space migration in F-SAFT method, the raw photoacoustic field $p(x, z=0, t)$ is firstly projected to the wavenumber-frequency domain (k_x, ω) , as illustrated in Equation (2.8). Further, to map the photoacoustic field from the (k_x, ω) space to the (k_x, k_z) space, a change of variable is performed with

$$\omega(k_z) = 2\pi c \cdot \text{sign}(k_z) \sqrt{k_x^2 + k_z^2}. \quad (2.11)$$

At last, with the relation of $d\omega = ck_z dk_z / \sqrt{k_x^2 + k_z^2}$, the calculation of the initial acoustic pressure field $p_0(x, z)$ is mathematically straightforward using

$$p_0(x, z) = \iint dk_x dk_z \frac{2ck_z}{\sqrt{k_x^2 + k_z^2}} P(k_x, z=0, \omega)e^{ik_x x} e^{-ik_z z}, \quad (2.12)$$

which is exactly the inverse 2D Fourier transform of the term

$$\frac{2ck_z}{\sqrt{k_x^2 + k_z^2}} P(k_x, z=0, \omega) .$$

Essentially, the major difference between the F-SAFT method and the Stolt method is the manner of migration. In the F-SAFT method, the photoacoustic field migration is performed from the $(k_x, 0, \omega)$ space to the (k_x, z, ω) space with a phase shift migration term $e^{\pm ik_z z}$, whereas in the Stolt method, the migration is performed from the (k_x, ω) space to the (k_x, k_z) space with a change of variable. When discretization goes to infinitely small, F-SAFT and Stolt migrations would provide the same imaging results. Whereas in the practical reconstruction problems, F-SAFT would provide slightly better imaging performances [40], which agrees well with the simulation results that an SNR improvement of 37.0 dB is obtained with the Stolt migration method, as shown in Figure 2.2(d).

2.3.4 Time reversal reconstruction algorithm

Analytical solution of the photoacoustic wave equation [equation (2.1)] in an acoustically homogeneous media can be easily calculated with before-introduced time/frequency domain reconstruction methods. However, these reconstruction methods loss efficiency in acoustically inhomogeneous media. According to the reciprocity theorem [121][122], a time reversed scalar field can be retrieved by retransmitting the measured signal in a temporally reversed order. In photoacoustic imaging, time reversal reconstruction is essentially a simulation model in which the planar ultrasound transducer array emits the experimentally measured photoacoustic signals in a temporally reversed manner. For example, the time reversal reconstruction is performed in a k-space pseudospectral method [119] subject to a time-variant boundary condition:

$$p_T(x, z = 0, t) = p(x, z = 0, T - t), \quad (2.13)$$

and the initial conditions:

$$\begin{aligned} p_T(x, z, t = 0) &= 0 \\ u_T(x, z, t = 0) &= 0, \end{aligned} \quad (2.14)$$

Figure 2.2(e) shows the reconstruction results using the time reversal reconstruction method, which shows a high imaging SNR of 47.4 dB. In general, in a relatively homogenous acoustic environment, the time reversal method always provides the best imaging performance since its back propagation provides a replica of the initial status of the photoacoustic generation. In an inhomogeneous situation, a priori knowledge of the inhomogeneity and iterative time-reversal processing are required to pursue an optimized reconstruction effect. In summary, the major properties of these four reconstruction methods are listed in Table 2.1 [123].

Table 2.1 Performance comparison among different photoacoustic reconstruction methods.

Methods	Back projection	F-SAFT	Stolt	Time reversal
SNR improvement	+	++	+	+++
Resolution	++	++	++	+++
Memory cost	+++	++	++	+
Time consumption	+	+++	+++	++

2.3.5 GPU-accelerated 2D synthetic aperture focusing algorithm

In this section, a two-dimensional synthetic aperture focusing (2D-SAFT) algorithm with a fast computing architecture is introduced [124]. Explained by the geometric modeling and Fourier acoustics theories, 2D-SAFT owns the narrower

post-focusing capability and better lateral resolution, compared to other 1D-SAFT techniques. Moreover, the 2D-SAFT algorithm is accelerated by a graphical processing unit (GPU) that reduces the long period of reconstruction (up to several hours) to only a few seconds. The proposed GPU-accelerated 2D-SAFT algorithm is demonstrated to outperform the previously reported 1D SAFT techniques in the aspects of improving the depth of focus, imaging resolutions, SNR, and computational efficiency.

Figure 2.3 Schematic of the 2D-SAFT reconstruction.

2.3.5.1 2D-SAFT algorithm

The idea underlying resolution enhancement by 2D-SAFT is based on the geometrical modeling and Fourier acoustics theories. As depicted in Figure 2.3, except the data points located at the edge of ROI, the photoacoustic waves are actually received by a virtual spherical aperture

$$P_{2D-SAFT}(n_x, n_y, t) = \sum_{i=1}^{N_x(n_x, n_y, t)} \sum_{j=1}^{N_y(n_x, n_y, t)} P(i, j, t - c\Delta t_{ij}), \quad (2.15)$$

where $P(i, j, t)$ is the raw signal received at ij 'th scan line, $P_{2D-SAFT}(n_x, n_y, t)$ is the post-focused signal at (n_x, n_y) after 2D-SAFT processing, $N_x(n_x, n_y, t)$ and

$N_y(n_x, n_y, t)$ respectively describe the number of virtual detectors included in the 2D synthetic aperture along the x direction and the y direction, which can be calculated by:

$$N_i(n_x, n_y, t) = \begin{cases} n_i + \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right), & \text{if } n_i \leq \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right) \\ 2 \cdot \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right) + 1, & \text{if } \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right) \leq n_i < N - \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right) \\ N - n_i + \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right) + 1, & \text{if } n_i \geq N - \text{ceil}\left(\frac{|ct - z_{VD}|}{2\Delta l \cdot F_N}\right) \end{cases} \quad (2.16)$$

where i can be replaced by x or y to indicate the different directions, Δl is the scanning step size, N is the number of scanning steps in the x or y directions, F_N is the F-number which can be roughly expressed as the ratio of the focal distance to the transducer diameter and is determined by the directivity of the focused transducer. A round-down function ceil is used, as $N_i(n_x, n_y, t)$ must be an integer. It's important to notice that instead of the full synthetic aperture size (*i.e.* signals from all the virtual detectors are utilized to construct the synthetic aperture at each position), depth-related numbers of virtual detectors ($N_x(n_x, n_y, t) \cdot N_y(n_x, n_y, t)$) are employed for optimized reconstructive performances and computational speed. Due to the limited view and directivity of the focused transducer, only parts of the virtual detectors contribute to the construction of the synthetic aperture efficiently. Using the out-of-view virtual detectors to construct synthetic aperture cannot give rise to improved imaging performances, on the other hand, may introduce unwanted artifact [125]. For example, at the depth of the focal plane ($t = Z_{VD} / c$), one single virtual detector constitutes the synthetic aperture itself, since $N_x(n_x, n_y, t) = N_y(n_x, n_y, t) = 1$. That is to say, there is no valid 2D-SAFT performed in the virtual-detector plane in the

proposed fast 2D-SAFT. In the previously reported SAFT algorithm, the uniform choice of the aperture size at different depths can be considered as employing the ideal point detectors with infinite F-number, however, which is unpractical for normal ultrasound transducers (including both flat transducer and focused transducer). Considering most of the energy would be received within a cone-shaped region, a finite F-number determined by the -6 dB directivity of the focused transducer is employed to avoid redundant computation while keeping the efficiency of the 2D-SAFT operation. Therefore, such an improved choice of the synthetic aperture size in the improved 2D-SAFT not only greatly improves the computational efficiency but also avoids unwanted artifacts.

In Equation (2.16), Δt_{ij} is the time delay applied to the received signal at the ij 'th scan, which is given by:

$$\Delta t_{ij} = \text{sign}(ct - z_{VD}) \frac{|ct - z_{VD}| - \sqrt{(ct - z_{VD})^2 + (n_x - i)^2 \Delta l^2 + (n_y - j)^2 \Delta l^2}}{c}. \quad (2.17)$$

Considering the normal cylindrical wavefront of the photoacoustic wave from a blood vessel, a 1D-SAFT was widely reported in previous literature [126]. In this sense, SAFT technique, in fact, is a method of geometric modeling of line-shaped virtual ultrasonic apertures at each data position. If we properly delay the received signals to be in-phase and then add them together, it is equivalent to manipulate the spatial position of the ultrasound detector to construct a synthesized aperture to focus on an arbitrary position.

For a focused transducer, the pressure pattern at the focal plane (in the Fresnel region) shares the same form with that in the Fraunhofer region for a planar transducer [127]. Therefore, the field pattern in the focal plane can be calculated by

$$\begin{aligned}
P(z) &= \frac{e^{ikz}}{z} \iint \sigma(x_a, y_a) e^{ik \frac{((x_a-x)^2 + (y_a-y)^2)}{2z}} dx_a dy_a \\
&= \frac{e^{ikz} e^{ik \frac{(x^2+y^2)}{2z}}}{z} \cdot \iint \sigma(x_a, y_a) e^{-ik \frac{xx_a + yy_a}{z}} dx_a dy_a.
\end{aligned} \tag{2.18}$$

where $\sigma(x_a, y_a)$ is the aperture function that indicates the 2D-projected shape of the acoustic aperture [128]. After simple variable substitution, Equation (2.18) can be reformed to

$$P(z) = \frac{e^{ikz} e^{ik \frac{(x^2+y^2)}{2z}}}{z} \mathfrak{F}\{\sigma(x, y)\} \Bigg|_{u_x = \frac{x}{\lambda z}, v_y = \frac{y}{\lambda z}}. \tag{2.19}$$

Noted that the amplitude distribution of the received acoustic signal in the focal plane is proportional to the Fourier transform of the aperture function. That is to say, the size of the focal point is diffraction limited by the distribution of $\mathfrak{F}\{\sigma(x, y)\}$ in the k-space. When a point (x, y) is located inside this acoustic aperture, $\sigma(x, y) = 1$; otherwise, $\sigma(x, y) = 0$. Thus, in the SAFT algorithm, the aperture function of the synthesized focused transducer would determine the focusing property.

Figure 2.4 illustrates the post-focusing patterns of different SAFT techniques with different synthetic apertures. Especially, for the raw data without any SAFT operation, an equivalent point-like aperture is firstly analyzed to provide a baseline with a broadband spectrum. Compared to the previously reported 1D-SAFT and cross-shaped SAFT, 2D-SAFT synthesizes a spherical-square shaped aperture with the narrowest Fourier spectrum in both x and y directions, which predicts the smallest focal spot of the synthesized aperture and thus the greatest and homogeneous lateral resolution in AR-PAM. For 1D-SAFT, only in the direction that is perpendicular to the line aperture, the Fourier spectrum is narrowed down, which coincides with the

results in previous literature [126]. To be noted that a cross-shaped SAFT synthesizes an incomplete spherical-square aperture with huge amounts of sidelobes in the Fourier spectrum, which explains the reason for the resolution degradation when compared to 1D SAFT in the B-scan direction.

Figure 2.4 (a) Geometric modeling of the 2D synthetic aperture algorithm. (b) 2D Fourier spectrum of the aperture function in different SAFT methods.

In addition to SAFT, a coherence factor (CF) is introduced as a weighting factor to neutralize the phase distortion induced by the acoustic inhomogeneity [129]. This factor can be deduced as the ratio of the coherent energy to the total energy of photoacoustic signals:

$$CF_{2D-SAFT}(n_x, n_y, t) = \frac{\left| \sum_{i=1}^{N_x(n_x, n_y, t)} \sum_{j=1}^{N_y(n_x, n_y, t)} P(i, j, z - c\Delta t_{ij}) \right|^2}{N_x(n_x, n_y, t) N_y(n_x, n_y, t) \cdot \left(\sum_{i=1}^{N_x(n_x, n_y, t)} \sum_{j=1}^{N_y(n_x, n_y, t)} |P(i, j, z - c\Delta t_{ij})|^2 \right)}. \quad (2.20)$$

Note a value of CF ranging from 0 to 1 can be obtained to indicate the level of coherence, in which a maximal value of “1” corresponds to the perfectly coherent

signal from each channel without any distortion. Combined this CF to the SAFT algorithm, one can finally express the CF weighted 2D-SAFT signal as:

$$P_{2D-SAFT-CF}(n_x, n_y, t) = P_{2D-SAFT}(n_x, n_y, t) \cdot CF_{2D-SAFT}(n_x, n_y, t). \quad (2.21)$$

For simplicity, “SAFT” used in the rest of the chapters all refer to the CF weighted SAFT.

2.3.5.2 Implementation of 2D-SAFT on GPU

In the proposed improved 2D-SAFT method, the reconstructed photoacoustic signal at a voxel grid (n_x, n_y, t) is the sum of all the acoustic pressure contributions weighted in a spherical aperture area. Since the aperture size $N(n_x, n_y, t)$, temporal delay Δt_{ij} , construction of the synthetic aperture $P_{2D-SAFT}(n_x, n_y, t)$, and CF weighting $CF_{2D-SAFT}(n_x, n_y, t)$ at different data positions can be calculated independently from Equation (2.16), (2.17) and (2.21) without any output conflict, the 2D-SAFT method is inherently data-parallel when decomposed into volumetric grid points.

Large-scale single-instruction multiple-data (SIMD) processes such as ultrasonic beamforming have been reported to enjoy tremendous speedup when parallelized on a GPU platform [130]. To facilitate the fast processing of the 2D-SAFT algorithm, besides the improved computational architecture, GPU programming can be further utilized, by which a middle-end GPU (GeForce GTX 980M, NVIDIA, USA) is programmed by the OpenCL framework to run the intensive parallel operations in this work. The open-source package Pyopencl, the OpenCL wrapper for python, enables to access the entire OpenCL parallel computation API. The compilation of the python code is automatically executed in the internal CPython interpreter.

Figure 2.5 (a) Data flow between the GPU and CPU. (b) Simplified code of the 2D-SAFT OpenCL kernel.

Figure 2.5(a) shows a serial diagram of the data transfer between the CPU and GPU. During the 2D-SAFT computation, the reshaped raw data are firstly transferred from the Host (CPU) to the GPU device memory and then stream into each processor core, in the form of the work items, to facilitate the kernel execution point by point in parallel. As shown in Figure 2.5(b), the OpenCL kernel is simply an inner loop for aperture size calculation, delay time calculation, CF weighting, and 2D-SAFT beamforming; while the OpenCL dispatcher is an outer loop over the grid points. Finally, the post-SAFT data are copied back to CPU for reshaping, storage, post-processing, and imaging display. To summarize, the reconstruction procedure consists of the following steps, as illustrated in Figure 2.5(b).

To fully take advantage of the locality of concurrent accesses to the pre-beamformed data, the raw photoacoustic data is partially staged in on-chip local memory to avoid frequent global memory transition. In addition, other optimization methods involving vector types is also applied, which reduces the global work

dimensions by increasing the usage of GPU register usage [131]. All optimizations are all contributed to amplifying the effective memory bandwidth available to the algorithm without any sacrifice of computational accuracy.

Figure 2.6 Simulated imaging reconstruction results with various SAFT methods. Point spread function (PSF) analysis is performed at three different positions ($y = -2.5$ mm, 0 mm, 2.5 mm).

2.3.5.3 Experimental demonstration of GPU-accelerated 2D-SAFT

Simulated imaging results before and after various SAFT operations are illustrated in Figure 2.6. Conventionally, a maximum amplitude projection (MAP) of the photoacoustic signals is preferred for explicit visualization of the volume rendered image. A time gain compensation (TGC) is adopted here to manually balance the imaging nonuniformity in the depth direction. Figure 2.6(a) displays the MAP images of the raw photoacoustic signals. As expected, though three ideal point absorbers can be roughly observed, the image suffers a low SNR and an inhomogeneous lateral resolution. To quantitatively characterize the imaging resolutions, normalized signal amplitude of each pixel along the white dashed lines ($y = -2.5$ mm, 0 mm, 2.5 mm) are plotted as black scatters in Figure 2.6(b). Then iterative Gaussian fitting is performed on these data to generate point spread function (PSF) at three different

depths. Lateral resolutions, defined as full width at half maximum (FWHM) of the interpolated PSF, are 290 μm , 498 μm and 740 μm , at the imaging depths of 0.5 mm, 1 mm, and 1.5 mm respectively. In line with the beam pattern of the spherically focused transducer, increasing the distance from the photoacoustic source to the virtual detector gives rise to the broadening of the acoustic beam width and deterioration of the lateral resolution.

After that, similar images processed by 1D-SAFT, cross-SAFT, and 2D-SAFT are shown in Figure 2.6(c), 2.6(e), and 2.6(g), respectively. The corresponding amplitude scatters and PSF at the same positions are plotted in the right column [Figure 2.6(d), 2.6(f), and 2.6(h)]. Slightly different from other SAFT methods, for 1D-SAFT, due to its inhomogeneous resolutions in the different directions, amplitude lines in all directions should be given to indicate the complete lateral resolution. Here, for simplicity, only the amplitude lines in the direction of the highest resolution (x direction, red lines) and the lowest resolution (y direction, green lines) are given in Figure 2.6(d).

Table 2.2 Comparison of the lateral resolution and imaging SNR with various SAFT methods.

Methods	Lateral resolution (μm) at different depths			SNR improvement (dB)
	0.5 mm	1.0 mm	1.5 mm	
Original	290	498	740	0.0
1D-SAFT	178/272	181/517	207/897	12.6
Cross-SAFT	284	281	268	13.4
2D-SAFT	171	188	184	21.2

Obviously, all the SAFT operations exhibit various degrees of resolution improvement and contrast enhancement, compared to the original MAP image. In order to have a quantitative comparison of the imaging performances between these SAFT methods, the -6 dB lateral resolution and SNR at imaging depths of 0.5 mm,

1.0 mm, 1.5 mm are benchmarked in Table 2.2. In which, the lateral resolution for 1D-SAFT is expressed in the form of “ x direction resolution/ y direction resolution”. For the lateral resolution, 1D-SAFT only improves the x -direction resolution, leaving the y -direction resolution unchanged, or even worse (*e.g.* 517 μm in 1.0 mm depth and 897 μm in 1.5 mm depth); In cross-shaped SAFT, though consideration is given to the resolution improvement in both x and y directions, whereas, an approximately 1.6 times resolution degradation in the x direction when compared to 1D-SAFT can be clearly observed at various depths; when it comes to 2D-SAFT, as expected, owing to the narrowest Fourier spectrum of the synthetic aperture, we get the best lateral resolution of about 180 μm , which is close to the -6 dB focal diameter at the focal plane for the given ultrasonic transducer (183 μm).

For imaging contrast and SNR, 2D-SAFT also outperforms all the other SAFT methods. The SNR analysis on the MAP image is employed as $SNR = 20\log(\frac{S_i}{\sqrt{\sigma_0^2}})$,

where S_i is the averaged brightness value (signal amplitude) of the three point absorbers, σ_0^2 is the variance of the background noise. Delaying and in-phase adding mechanism of the SAFT operation provide an averaging effect on the received photoacoustic signals. From the original microscopy image to the 1D line-shaped SAFT and cross-shaped SAFT images, and finally to the 2D-SAFT image, the increase of the aperture size leads to an increased number of signal average, leading to better suppression of noise. Therefore, in this simulation, 2D-SAFT shows a better lateral resolution and imaging SNR compared to all the reported 1D-SAFT techniques.

Figure 2.7 Phantom imaging results with various SAFT methods.

To further investigate the performance of 2D-SAFT on arbitrary-shape sources instead of only ideal point absorbers, phantom imaging experiments are carried out (Figure 2.7). TGC weighted MAP image of the original PAM, 1D-SAFT PAM, cross-SAFT PAM, and 2D-SAFT PAM are plotted in Figure 2.7(a)-(d), respectively. Owing to the low SNR and lateral resolution at the out-of-focus region, the character “2D SAFT” is blurred. Notably, after various SAFT operations, both lateral resolution and imaging contrast are substantially improved. It’s worthy to note that some edges in Figure 2.7(b) seem to be sharper than that in Figure 2.7(c), especially for the edges that are perpendicular to the x direction (the direction of 1D-SAFT), which is consistent with the former analysis in the theory section. However, the image is to some extent distorted due to inhomogeneous resolutions at different locations and directions, which makes it difficult to match the MAP image to the original

pattern of the phantom. Cross-SAFT performs much better in the aspects of the resolution homogeneity [Figure 2.7(c)], yet resolution improvement is not so impressive compared to the results of 1D-SAFT. On the other hand, intensive artifacts around the real optical absorbers in the phantom can't be effectively removed. 2D-SAFT provides the best visualization among all these methods. For example, the intact letter "S" can be clearly identified only in Figure 2.7(d), however, only part of it can be obtained in Figure 2.7(a)-(c). Figure 2.7(j) also gives the volume rendered image after the 2D-SAFT operation to illustrate the distribution of the phantom.

Lateral resolutions are quantified by imaging the sharp edge of the letter "T" within the white dashed boxes. The edge spread function [ESF, Figure 2.7(e)] is calculated by averaging the perpendicular amplitude lines along the sharp edge (shown in the inset). Taking the derivative of the interpolated ESF and then Gaussian curve fitting yields the line spread function [LSF, Figure 2.7(f)-(i)]. In both ESF and LSF, 2D-SAFT shows the narrowest width and lowest standard deviation, which indicates the best lateral resolution and imaging SNR. Consistent with the simulated results showed in Table 2.1, 2D-SAFT exhibits the best SNR improvement of 18.6 dB and the lateral resolution of 190 μm . Such results demonstrate the superiority of 2D-SAFT over the other SAFT techniques, in the aspects of not only SNR enhancement but also resolution improvement. Because ESF analysis is only carried out in the x and y direction, the local resolution is comparable to that of cross SAFT, while the realistic resolution is ranging from 630 μm to 202 μm . With the narrowest Fourier spectrum of in both x and y directions, 2D-SAFT provides a homogenous and the greatest spatial resolution among all the SAFT operations. In addition, an increased number of virtual detectors and thus increased aperture area facilitate a much higher SNR improvement.

Both simulated and experimental results demonstrate that 2D-SAFT in AR-PAM could provide dramatically improved lateral resolution and imaging SNR. However, taking account of the dramatically increased parallel computation from 1D to 2D SAFT, computational speed is highly limited under normal CPU processing, even for the improved computational architecture in this work. For microscopy imaging over a range of $10 \times 10 \text{ mm}^2$ with 610.3 MB ($400 \times 400 \times 1000 \times 4.0$ bytes) volumetric data, 1D-SAFT costs about 10 minutes using the normal CPU processing. Being equivalent to two perpendicular 1D-SAFT operations, cross-shaped SAFT costs about 17 minutes, which is approximately twofold consuming time of 1D-SAFT. Compared to the normal mechanical scanning time of about several minutes, sacrificing such comparable time for SAFT operations to improve the spatial resolution and SNR is definitely worthwhile. However, when it comes to 2D-SAFT, extremely prolonged computational cost (> 2 hours) becomes the bottleneck.

Figure 2.8 Time consumption of the 2D-SAFT implemented in CPU and GPU.

By employing 2D-SAFT with improved computational architecture, the operation time of 2D-SAFT reduces more than three times to be of about 4013.6 s. Further using parallel GPU processing, the computation time is spectacularly shortened to be only 3.13 s. As Figure 2.8 shows, the initialization progress including obtaining the device, creating the context, creating a command queue, and allocating memories only

occupies 323 ms. Data transfer time from CPU to GPU and from GPU to CPU are approximately 103 and 101 ms, respectively, corresponding to a data transfer speed about 5.9 GB/s between CPU and GPU memory. The processing duration of the OpenCL kernel is 2602 ms, which is the longest process in the overall process, during which SAFT and CF calculations dominate the time consumption due to a large number of multiplication operations. Therefore, accelerated by the GPU programming, the time duration for the 2D-SAFT process can be reduced to several seconds, which is negligible even compared to the imaging time of the fastest voice-coil mechanical scanning microscopy system [132].

2.3.5.4 Conclusion

This section suggests to post-focus the photoacoustic microscopy image by using the GPU-accelerated 2D-SAFT method. By implementing dynamic focus among each position in the whole volume, a large range of depth of focus can be realized with relatively homogeneous lateral resolutions. Based on the Fourier acoustic analysis, 2D-SAFT provides the narrowest Fourier spectrum of the aperture function, which gives rise to the best post-focusing ability. A good agreement is found between the simulation and experimental studies, both demonstrate that GPU-accelerated 2D-SAFT exhibits high computational efficiency and superior imaging performances.

In this work, a 20MHz 0.25 NA focused transducer is used in AR-PAM to record the raw data. A higher-frequency ultrasonic transducer (up to hundreds of megahertz [133]) with larger NA can be employed to further improve the focusing performance. However, accompanied by the higher center frequency, the penetration depth in the biological tissue is restricted (*e.g.* 50 MHz focused transducer [134]). In addition, a smaller F-number beyond the directivity of the focused transducer can be employed to further improve the imaging performance, since the transducer can still detect the

signals outside the directivity region, though with relatively low intensities. However, such a choice of F_N may slightly increase the computational cost. Some other methods like deconvolution and delay multiply and sum can be additionally leveraged in this 2D-SAFT algorithm to further improve the imaging performance [135][136]. On the other hand, SAFT techniques also have their internal limitations. AR-PAM employing a focused ultrasound detector always suffers the limited view artifacts, which can't be well eliminated by using the general SAFT methods. Recently, to facilitate clear visualization of the descending microvasculature propagating at steep angles, Deán-Ben *et al.* have proposed to employ a hemispherical array with broad 180° tomographic coverage to avert image artifacts associated with limited-view acquisition geometries [137]. This inspires us to change the scanning method and adopt full-angle synthetic aperture focusing to further improve the imaging performance in the future [138].

Chapter 3. An All-in-one Handheld Photoacoustic 3D Imager

In this chapter, an all-in-one handheld photoacoustic 3D imaging system is developed and presented [139]. In this handheld imager, all the optical units, acoustic units, and photoacoustic matching unit are integrated into a single handheld probe (*i.e.* all-in-one) with a compact size of about $160 \times 64 \times 40 \text{ mm}^3$. In section 3.1, state-of-the-art 3D photoacoustic imaging systems are reviewed. In section 3.2, the design and development of the handheld 3D imager, in terms of the optical module design, acoustic module design, photoacoustic matching layer design, and backend data acquisition, are presented. Section 3.3 introduces the fast imaging reconstruction algorithm—layered phase shift migration method in photoacoustics, which is dedicatedly designed for the stratified condition in the developed handheld 3D imager. In section 3.4, 3D handheld photoacoustic imaging is experimentally demonstrated in *in-vitro* needle biopsy and temperature mapping during photothermal therapy. In section 3.5, some important issues with regard to system stability, power management, and laser safety are discussed.

3.1. Introduction

In recent decades, photoacoustic imaging has been demonstrated as a powerful multi-wave imaging modality that combines optical excitation and ultrasonic detection. In photoacoustics, biological tissues are irradiated by a pulsed laser to achieve localized optical absorption and heating. The induced instantaneous temperature rise leads to a pressure rise via thermoelastic expansion and then produces ultrasound emission. The generated ultrasonic waves are detected by ultrasound transducers to reconstruct an image, which reveals the distribution of the optical absorbers at the region of interest (ROI). Integrating the rich optical contrast

and the high ultrasonic resolution at depth, photoacoustic imaging is a promising tool for a wide range of biomedical applications [140]-[142].

Figure 3.1 (a-e) State-of-the-art 3D photoacoustic imaging systems. (f) Developed handheld photoacoustic 3D imager. PA: photoacoustic; DAQ: data acquisition system.

In both scientific and preclinical studies, three dimensional (3D) medical visualization of physiology and pathology is of great interest, especially when associated dynamic phenomena in 3D space, *e.g.* needle biopsy [143], targeted drug delivery [144], cell kinetics [145], cardiac activities [146], hyperthermia [147], and other time-variant events. 3D photoacoustic imaging has two main-stream implementations—photoacoustic microscopy (PAM) and photoacoustic computational tomography (PACT). In 3D PAM, by scanning the focused transducer [acoustic resolution photoacoustic microscopy (AR-PAM) in Figure 3.1(a)] or the focused laser irradiation [optical resolution photoacoustic microscopy (OR-PAM) in Figure 3.1(b)] in a two 2D horizontal plane [148], volume rendered images can be straightforwardly extracted by simple post-processing (*e.g.* 2D synthetic aperture focusing techniques [57]). The other implementation—PACT, based on the inverse reconstruction, requires wide-field light illumination and acoustic detection at multiple locations. 3D PACT can be configured with a scanning linear transducer

array [Figure 3.1(c)] [76][107][149], a full-ring transducer array [Figure 3.1(d)] [108][150], or their 3D scanning equivalents [151]. Alternatively, a hemispherical array of ultrasound detectors can be employed to avoid motorized scanning for high-speed 3D imaging [Figure 3.1(e)] [65][67][78][152][153]. Other 3D PACT implementations include using fiber-based line detector [154], 2D matrix array [61], spherical matrix arrays [137], acoustic lens system [155] and planar Fabry–Perot polymer film sensing interferometer [156]. These recent advances have greatly pushed the photoacoustic technique towards a 3D real-time imaging modality and a wide variety of applications in biomedical research.

Yet, currently available 3D photoacoustic systems are not portable and not suitable for flexible handheld operations as the commercial ultrasound handheld imager. Till now, designing a portable 3D system supporting handheld operations is a nontrivial task, which is partly due to the difficulty of miniaturizing the bulky high-power laser system, and partly due to the complexity of the acoustic receiving system.

(1) Optically, to generate photoacoustic signals efficiently for 3D imaging, a high energy (millijoules to joules per pulse) pulsed laser with sub-microsecond pulse durations is generally required. In addition, to achieve adequate penetration depth, it is desirable to use a wavelength in the near infrared (NIR) window (600 to 1350 nm), where biological tissues are relatively translucent. These requirements can be easily satisfied by using a Q-switched Nd: YAG laser (1064 nm) or a tunable OPO pulsed laser. However, these lasers are generally bulky, costly, and not to mention the high requirement of the affiliated optical system, including the vibration-isolation optical tables, trivial fiber optic alignment, *etc.* To minimize the system size, some solutions using compact diode array (*e.g.* diode stack [69][157][158], LED arrays [31]) are also adopted. However, due to their low optical power (0.56 mJ in [69] and 20 mW in

[159]) and off-axis illumination design, only 2D cross-sectional imaging along the depth direction (B-mode) is available. Such an imaging mode may not be suitable to monitor the dynamic activities in 3D space. For further realization towards 3D imaging, mechanical scanning of the whole photoacoustic probe is required as employed in Ref. [76] [Figure 3.1(c)]. (2) On the acoustic side, scanning based 3D imaging methods (*e.g.* AR-PAM, OR-PAM, and 3D PACT with a scanning array) are time-consuming, which greatly hampers their real-time application. More recent 3D photoacoustic imaging systems employed matrix arrays (*e.g.* a hemispherical array, a full-ring array, or an arc-shaped array [79]) without mechanical scanning, nevertheless, did not support flexible and rough handheld operations as the commercial B-mode ultrasound imager. Moreover, the acoustic coupling between the ultrasound transducer array and the imaging tissue is a nontrivial task, either in the hemispherical or full-ring implementations. Thus, additional water coupling in the form of a water tank, a polyvinyl chloride membrane covered water packet [79], or a water cage [67] is still necessary. Therefore, though these tomographic implementations are especially suitable for brain imaging of small animals [67] and breast imaging (named mammography) [160][161], dedicated chamber design and susceptible acoustic coupling hinder their translation towards handheld applications. Here, with the aim of clinical translation of the photoacoustic technique, a handheld imager for 3D photoacoustic imaging is proposed and developed. In this 3D imager, the whole optical module (including laser source) and acoustic receiving module are integrated into a single handheld probe. The key breakthroughs of this work are the miniaturization of the photoacoustic 3D imager to be fully portable and its handheld capability for dynamic (temporally and spatially) 3D imaging, in which the imaging probe can be handheldly move to any ROI for tracking dynamic activities in 3D, as

illustrated in Figure 3.1(f). Besides, since the traditional photoacoustic imaging reconstruction methods will not be applicable for the special layered imaging environment in the designed 3D imager, a dedicated reconstruction is developed based on a fast-phase migration (PSM) method. System performances are tested in *in-vitro* handheld photoacoustics guided needle biopsy and photoacoustic thermal imaging. Afterward, imaging performances in the aspects of system stability, power management, and safety issues for the developed handheld 3D imager is discussed.

3.2. Handheld Photoacoustic System Design

The developed portable photoacoustic system is illustrated in Figure 3.2. A handheld probe is designed to fully integrate all the optical components (including a laser source, a trigger circuit, and a laser power supply) and acoustic components (including a compact 2D transducer array and an optical/acoustic matching layer). The handheld photoacoustic probe is about $160 \times 64 \times 40 \text{ mm}^3$, which is slightly larger than a commercial ultrasound linear array (*e.g.* $120 \times 38 \times 16 \text{ mm}^3$ for ATL L10-5 [162]). The overall weight of the handheld photoacoustic probe is about 171 g.

Figure 3.2 (a) Schematic of the handheld photoacoustic 3D imager with (b) a compact diode laser and (c) a 2D matrix array. (d) Photograph of the developed handheld photoacoustic 3D imager.

3.2.1 Optical module design

To pursue high-energy optical irradiation for 3D photoacoustic imaging, a gas laser, a liquid laser or a solid-state laser is typically employed as the optical source, which unfortunately suffers from bulky system size and high cost, and generally requires careful maintenance. Semiconductor laser, on the other hand, is especially desirable for developing a portable system because of its compact size, low cost, and low voltage requirements.

To this end, a high-power pulsed laser diode (Quantel QD-Qxy10-ILO, France) is employed as the optical source, in which the laser driver and diode bar are integrated into a very compact body ($11 \times 6 \times 3.6 \text{ cm}^3$). It provides a 120 ns pulse duration at 808 nm and a pulse energy of 1.3 mJ with a repetition rate of up to 5 kHz. The laser diode generates a rectangular beam which diverges with an angle of ~ 10 degrees and ~ 0.7 degrees along the slow and fast axes at full width at half maximum (FWHM), respectively. A cylindrical lens (Thorlabs LJ1695RM, USA) is tightly placed under the laser diode to reshape the beam to be a quasi-collimated light. The light is further focused by an aspherical condensing lens (Thorlabs ACL25416U, USA) and guided through the center hole of the 2D ultrasound transducer array and finally irradiates the biological tissue, as shown in Figure 3.2(a). To avoid potential optic damage and maintain acceptable optical fluence, a transparent polydimethylsiloxane (PDMS) layer is attached under the 2D matrix array for beam expansion.

Therefore, a highly integrated laser diode and two lenses constitute the whole optical module. Light attenuation in the lens group is measured to be about 5 %, while 3% in the PDMS layer, which ultimately provides pulse energy of 1.13 mJ with an optical transmission efficiency of 87 % in total. Benefiting from the high electrical-to-optical efficiency (25 % for the laser diode) and the high optical transmission

efficiency (87 %), a battery can be employed to substitute the normal bulky power supply for the laser system. Here, a 12 V, 240 mAh rechargeable lithium-ion polymer battery is employed for further miniaturization of the photoacoustic system.

3.2.2 Acoustic module design

The ideal ultrasound transducer array for 3D photoacoustic imaging should provide high resolutions, an excellent sensitivity, a wide bandwidth, and a miniaturized size [163]. To fulfill these requirements, a compact 2D piezoelectric micro-machined ultrasound transducer (PMUT) array (Doppler, China) is custom designed. PMUT transducers offer a miniaturized size, and easy integration with front-end electronics. It can be easily fabricated with a broad range of sizes and arbitrary array geometries such as the ring array or flexible array, which will be particularly suitable for 3D photoacoustic imaging.

The geometry of the custom-made 2D matrix array is illustrated in Figure 3.3(a) with its photograph shown in Figure 3.2(c). The 2D matrix array is about 15×80 mm², with a thickness of only 3 mm. It consists of 72 detector elements that are arranged within a 9×9 grid, as illustrated in Figure 3.3(a). The active aperture contains a circular opening (occupying the center 3×3 grid) at the center of the square aperture with a diameter of 2 mm for optical illumination, enabling the coaxial optical illumination and photoacoustic detection. The center frequency of the 2D matrix array is 2.25 MHz, and the frequency bandwidth is larger than 60 % (– 6 dB) in the transmit/receive mode. The aperture size of each piezo-composite element is 1.0 mm in diameter, with a 1.07 mm pitch.

3.2.3 Photoacoustic matching layer design

Followed by the 2D matrix array, the PDMS layer ($20 \times 20 \times 6 \text{ mm}^3$) is tightly attached under the array aperture. This PDMS layer is essential for laser safety, acoustic-field homogeneity, and efficient overlap between the optical field and the acoustic sensitivity pattern. Details are given below:

Figure 3.3 (a) Geometry of the handheld 3D imager. (b) Monte Carlo optical simulation results. (c) *k*-wave acoustic simulation results. (d) Resultant photoacoustic sensitivity pattern.

(1) The DPMS layer serves as an optically transparent optical delay line (ODL) [164] to diverge the laser beam before it reaches the biological tissue, thus to satisfy the ANSI safety standards [165]. Based on the geometric model [Figure 3.3(a)], Monte Carlo simulation [166] is performed to calculate the optical fluence pattern at the tissue interface [Figure 3.3(b)]. When the photoacoustic probe directly contacts the tissue surface without using the intermediate PDMS layer, due to short optical path length away from the focal point, laser fluence at the tissue surface can be calculated up to 50 mJ/cm^2 , which is highly larger than the maximal permeable laser fluence (33.7 mJ/cm^2) [165]. In the developed handheld photoacoustic 3D imager, owing to the beam expansion in the PDMS layer (blue square), laser fluence at the tissue interface can be decreased to 5 mJ/cm^2 . In addition, the PDMS will contribute

to a relatively homogeneous optical field, in which a maximal fluence difference of about 4.7 dB is observed within the field of view (FOV) when the observation plane is 1 mm below the tissue interface.

(2) The DPMS layer also serves as an acoustically transparent acoustic delay line (ADL) [167] to avoid inferior imaging performances in the near field. Since the array aperture includes a 3×3 opening for optical illumination, homogeneity of the acoustic sensitivity in the near field is highly affected. Figure 3.3(c) illustrates the acoustic beam pattern of the 2D matrix array calculated by *k*-wave simulation toolbox [119]. Without the PDMS layer, acoustic sensitivity variation within the FOV is calculated to be larger than 12 dB. Such acoustic inhomogeneity would cause severe imaging artifacts and greatly influence the imaging performance in the near field. When the PDMS layer is employed, the biological tissue to be imaged would be shifted to the far field, providing a relatively homogeneous acoustic beam pattern (sensitivity variation < 2.6 dB).

(3) The PDMS can provide an excellent overlap between the optical illumination volume and the acoustic detection volume, offering a relatively homogeneous photoacoustic environment [Figure 3.3(a)]. To study the photoacoustic detection sensitivity, the optical illumination pattern and the acoustic beam pattern are combined to form the photoacoustic sensitivity map [Figure 3.3(d)]. At the observation plane, the difference of the photoacoustic sensitivity within the FOV is calculated to be 6.9 dB when employing the PDMS layer, whereas 58.9 dB when the PDMS layer is not used.

(4) For some photoacoustic applications (*e.g.* temperature mapping), the PDMS layer serves as a thermal insulator to prevent the human's temperature interfering the transducer sensitivity.

There are several reasons why we chose PDMS. Firstly, PDMS is optically and acoustically translucent. Secondly, PDMS is simple to manufacture with low cost, and it is nontoxic during preparation and application [168]. Thirdly, its optical property, acoustic property, and mechanical property are stable for months and even years, and it is durable against rough handling during handheld operations. And in addition, its exceptionally fine geometry (in the order of tens of micrometers) enables the smoothness and thickness to be well controlled. In this work, the PDMS layer is prepared by the standard soft lithography [168]. It has a speed of sound of 973 m/s and a density of 1294 kg/m³. Optical attenuation in the 6 mm PDMS layer is measured to be 3 % at 808 nm wavelength and the acoustic attenuation coefficient is measured to be about 1.14 dB/(cm·MHz)⁻¹.

3.2.4 Data acquisition and image display

An Arduino MCU (Arduino Micro) provides a 5V TTL (Transistor-Transistor Logic) signal to synchronize the data acquisition (DAQ) with the laser excitation. A portable SonixDAQ (Ultrasonix Inc. Raymond, Canada) collects the photoacoustic signals and provides simultaneous access to the pre-beamformed RF data to the upstream computer for image formation. The DAQ system provides an LNA amplifier (14 dB), a VGA amplifier (30 dB), and a 40 MHz analog-to-digital (ADC) converters. A general personal computer (PC) coordinates the digital data storage, image reconstruction, and 3D image display [Figure 3.1(f)].

3.3. Phase Shift Migration Method for Fast Photoacoustic Reconstruction

In the traditional PACT, the transducer is immersed in water or directly contacted with the biological tissue. Therefore, the imaging object and surrounding medium are

assumed to have the same speed of sound. However, in the developed handheld 3D imager, the introduction of the PDMS layer violates such an assumption. As a result, image reconstruction with the traditional time domain [118] and frequency domain [120] methods may lead to severe distortions and artifacts.

Time reversal method [122], though an effective reconstruction method for heterogeneous medium, is computationally intensive and memory hungry [169], especially for 3D reconstruction applications. The model-based approach is based on a discrete representation of the forward acoustic problem. Similarly, this iterative process also suffers from relatively large memory usage and computational cost [170]. Therefore, to solve the challenging heterogeneous problems in the developed handheld 3D imager, a PSM based reconstructive method for multilayer photoacoustic imaging is dedicatedly proposed in this work.

In the 3D handheld imager, the reconstruction process can be modeled as a two-layer acoustic propagation problem, as illustrated in Figure 3.4(a). Assuming the 2D matrix array is placed in the horizontal plane at the depth z_0 , the first layer (PDMS layer) is located in the range from z_0 to z_1 with a consistent speed of sound c_{PDMS} . The second layer ($z > z_1$) is the biological tissue (speed of sound: c_{tissue}), where photoacoustic waves are generated. Using $p(x, y, z, t)$ to denote the time-varying acoustic field, acoustic wave propagation can be described with the general acoustic wave equation:

$$\begin{aligned} \left(\nabla^2 - \frac{1}{c_i^2} \frac{\partial^2}{\partial t^2} \right) p(x, y, z, t) &= 0, \\ c_i &= \begin{cases} c_{PDMS} & \text{for } z_0 < z \leq z_1 \\ c_{tissue} & \text{for } z > z_1 \end{cases} \end{aligned} \quad (3.1)$$

subject to the initial condition:

$$p(x, y, z, t=0) = \beta c_{tissue}^2 A(x, y, z) / C_p, \quad (3.2)$$

where C_p is the heat capacity, β is the isobaric volume expansion coefficient, the speed of sound c_i equals to c_{PDMS} and c_{tissue} , for $z_0 < z \leq z_1$ and $z > z_1$, respectively.

$A(x, y, z)$ is the absorbed optical energy density to indicate the contrast distribution in 3D space.

Figure 3.4 Flowchart of the phase shift migration (PSM) method for photoacoustic reconstruction.

Let $p(x, y, z = z_0, t)$ denote the time-varying field received by the 2D matrix array.

Figure 3.4(b) shows an example of the volume rendered photoacoustic wavefield from 9 photoabsorbers. Some data absence in $p(x = 0, y, z = z_0, t)$ corresponds to the 3×3 optical opening at the center of the 9×9 square aperture.

This acoustic field $p(x, y, z = z_0, t)$ is observed in the horizontal plane at the depth z_0 , and our aim is to use such a received field to determine the initial photoacoustic

pressure field at the time of laser excitation, *i.e.* $p(x, y, z, t=0)$, and then the distribution of optical absorption $A(x, y, z)$. As will be described below, this reconstruction can be realized by the fast PSM method in the frequency domain.

The PSM method, based on the exploding reflector model, was originally proposed in the nondestructive evaluation field for testing stratified structures [171]. In the migration process, the recorded pressure waves $p(x, y, z = z_0, t)$ are firstly projected to the wavenumber-frequency domain:

$$p(x, y, z = z_0, t) = \iiint P(k_x, k_y, z = z_0, \omega) e^{ik_x x} e^{ik_y y} e^{-i\omega t} dk_x dk_y d\omega, \quad (3.3)$$

where k_x and k_y represent the wavenumbers of x and y respectively, and ω represents the angular frequency. Figure 3.4(c) provides the volume rendered image of the $P(k_x, k_y, z = z_0, \omega)$. Since the power spectrum of the recorded photoacoustic field is band-limited with a cutoff frequency far below the Nyquist frequency, data truncation in the frequency domain (ω) can be performed for data compression.

On the other hand, Equation (3.1) written in the wavenumber-frequency domain (k_x, k_y, ω) is a second-order ordinary differential equation:

$$\frac{d^2 P(k_x, k_y, z, \omega)}{dz^2} = -k_{i,z}^2 P(k_x, k_y, z, \omega), \quad (3.4)$$

where $k_{i,z}$ is the wavenumber in the z direction and satisfies the relationship $(\omega/c_i)^2 = k_x^2 + k_y^2 + k_{i,z}^2$. Therefore, the characteristic solution of Equation (3.4) has the form $P(k_x, k_y, z + dz, \omega) = P(k_x, k_y, z, \omega) e^{\pm ik_{i,z} dz}$, which relates the acoustic field at z with that at $z + dz$ by a phase shift. This equation provides a hierarchy of migration methods to extrapolate the received acoustic field to the planes at any depth based on

different approximations of $k_{i,z}$. This is the essence of the PSM method, as introduced by Olofsson in Ref. [171] and outlined in the flowchart of Figure 3.4.

In the following, PSM reconstruction of acoustic waves in the PDMS layer (first layer) and the tissue layer (second layer) is performed in sequence. Firstly, consider the PDMS layer ($z_0 < z \leq z_1$). As the photoacoustic sources are distributed in the tissue layer ($z > z_1$), only the up-traveling components should be considered for field extrapolation. This gives us [172]

$$P(k_x, k_y, z, \omega) = P(k_x, k_y, z_0, \omega) e^{ik_{PDMS,z}(z-z_0)}, \text{ for } z_0 < z \leq z_1. \quad (3.5)$$

Specifically, at the layer interface z_1 , acoustic field can be calculated as

$$P(k_x, k_y, z = z_1, \omega) = P(k_x, k_y, z_0, \omega) e^{i(z_1-z_0)\sqrt{k_x^2+k_y^2-\omega^2/c_{PDMS}^2}}. \quad (3.6)$$

Compared to $P(k_x, k_y, z = z_0, \omega)$, only a phase shift term $e^{i(z_1-z_0)\sqrt{k_x^2+k_y^2-\omega^2/c_{PDMS}^2}}$ is appended into the $P(k_x, k_y, z = z_1, \omega)$. Therefore, though acoustic field has changed a lot when spreading from z_1 to z_0 , the power of the field spectrum keeps unchanged, as shown in Figure 3.4(c-d).

Secondly, PSM is performed in the second layer ($z > z_1$). Neglecting the acoustic transmission factors between the two layers, field extrapolated at depth z_1 is used as the boundary condition defining the solution within the tissue layer. By proceeding the extrapolation in a similar way in the tissue layer, we find that the acoustic field at any depth for $z > z_1$ can be expressed as

$$P(k_x, k_y, z, \omega) = P(k_x, k_y, z = z_0, \omega) e^{i\sqrt{k_x^2+k_y^2-\omega^2/c_{PDMS}^2}(z_1-z_0)} e^{i\sqrt{k_x^2+k_y^2-\omega^2/c_{tissue}^2}(z-z_1)}, \text{ for } z > z_1. \quad (3.7)$$

The multiplication term $e^{i\sqrt{k_x^2+k_y^2-\omega^2/c_{PDMS}^2}(z_1-z_0)}$ and $e^{i\sqrt{k_x^2+k_y^2-\omega^2/c_{tissue}^2}(z-z_1)}$ represent the phase shift in the PDMS layer and the tissue layer. It is from this relation that PSM takes its name, as in ultrasound imaging [171]. Note that in the extrapolated 4D data structure [Figure 3.4(e)], each frame at an extrapolation depth corresponds to a 3D wavefield in the wavenumber-frequency domain. Therefore, Equation (3.7) describes the relation between the observed wavefield in the wavenumber-frequency domain and the extrapolated wave field at any depth (in the form of 4D data structure). Hence, the initial acoustic pressure field $p(x, y, z, t = 0)$ can be reconstructed by

$$p(x, y, z, t = 0) = \iiint P(k_x, k_y, z = z_0, \omega) e^{ik_x x} e^{ik_y y} e^{i\sqrt{k_x^2+k_y^2-\omega^2/c_{tissue}^2}(z-z_1)} e^{i\sqrt{k_x^2+k_y^2-\omega^2/c_{PDMS}^2}(z_1-z_0)} dk_x dk_y d\omega, \text{ for } z > z_1. \quad (3.8)$$

This integral can be executed by first integrating the extrapolated wavefield over ω [Figure 3.4(e) to 3.4(f)], followed by the inverse Fourier transform over k_x and k_y [Figure 3.4(f) to 3.4(g)].

In summary, the PSM reconstruction algorithm is executed by decomposing the observed acoustic signal into a set of harmonic plane wave components, performing the extrapolation separately for each component in each layer, and superimposing the results. It is important to note that though 2D matrix array has an optical opening at the center of the aperture, optical contrast information in the center area can be reconstructed successfully. This is attributable to the PDMS intermediate layer by providing an efficient and homogenous overlap between the optical illumination and acoustic detection [Figure 3.3(d)]. Therefore, when the wavefield is projected to the wave-number frequency domain, the incomplete aperture area induced data absence can be compensated by the acoustic signals received from other surrounding transducer elements with a relatively homogeneous sensitivity pattern [173].

Photoacoustic simulation in 3D space is executed using *k*-wave simulation toolbox [119]. Figure 3.2(g) shows the simulation results using the multiple-layer PSM method, in which nine absorbers at three different depths can be faithfully retrieved in the volume rendered image and its 2D projection. The lateral resolution and the axial resolution are estimated to be 0.69 mm and 0.54 mm, respectively. For comparison, images reconstructed by the conventional DAS method with a consistent speed of sound ($c=1540$ m/s) are presented in Figure 3.2(h). A parabolic trajectory of the photoacoustic signal is still visible, indicating imperfect beamforming with the wrongly assumed speed of sound. To compensate for the low speed of sound in the PDMS layer, DAS reconstructions with different speed of sound values are also performed. As expected, though nine ideal point absorbers can be roughly observed, all images are highly blurred with a low signal to noise ratio (SNR) and degraded resolutions.

The phase-shift formulation of migration enables elegant data parallelism [173]. Benefit by the fast implementation in the frequency domain, the time for image generation using a standard computer processing unit CPU (Intel® Core™ i7 5800U) is about 1.7 s (0.27 s for data acquisition, 1.42 s for image reconstruction). The simulation results preliminarily demonstrate that the PSM based reconstruction method is suitable for the developed handheld photoacoustic 3D imager.

3.4. Imaging Performance Characterization of the Handheld

Photoacoustic Imager

3.4.1 Handheld photoacoustics guided needle biopsy

Photoacoustics guided needle operation has been widely used in diagnostic biopsy procedures [174] and therapeutic agent injection [70], where the strong photoacoustic

response provides the dynamic information of the metallic needle (*e.g.* position, orientation, and trajectory) in 3D space. In this sense, a 3D photoacoustic imaging system supporting flexible handheld operations is in urgent demand for photoacoustic needle guidance.

In this work, 3D photoacoustic needle guidance is demonstrated with a 30 G needle (0.3 mm diameter), which is inserted into an *in-vitro* fresh porcine tissue at a slight downward angle ($\sim 15^\circ$). As the metallic needle is gradually inserted into the porcine tissue, it is photoacoustically tracked in real-time with the developed handheld 3D imager. In particular, with the aim of fully capturing the insertion dynamics, a change of FOV is performed by handheldly shifting the 3D imager along the direction of the needle movement. Several snapshots of 3D photoacoustics guided needle insertion are shown in Figure 3.5, where the top row corresponds to the photoacoustic images captured at the start position [Figure 3.5(a)] and the bottom row corresponds to the photoacoustic images captured at the second position after the handheld imager is right-shifted [Figure 3.5(h)]. All photoacoustic images are reconstructed from the RF data that are averaged over four laser pulses to improve the image SNR.

Figure 3.5 3D photoacoustics guided needle biopsy with a handheld operation.

Firstly, at the start position [Figure 3.5(a)], when the metallic needle is just inserted into the porcine tissue, only a small tip of the needle is captured, as shown in Figure 3.5(b). Afterward, with the needle moving forward and deeper, a larger portion of the needle body enters the FOV of the 3D photoacoustic imager [Figure 3.5(c) to 3.5(f)]. Some artifacts (caused by the limited-view detection and motion effect) may be present [Figure 3.5(c) and 3.5(e)], nevertheless, they are not severe and will not be problematic for tracking needle dynamics.

Since the effective FOV of this handheld photoacoustic 3D imager is approximately determined by the aperture area of the 2D matrix array [Figure 3.3(d)], the needle tip would be out of the FOV if the needle inserts further, as shown in Figure 3.5(g). Therefore, the handheld photoacoustic 3D imager is manually shifted from left to right about 5 mm [Figure 3.5(h)]. When the handheld imager is moving, due to unstable acoustic coupling and uncorrelated frame averaging, several frames of 3D images suffer from severe artifacts. No useful photoacoustic information is obtained during this period. With the handheld imager stabilizing at the second position, the FOV of the handheld imager is also right shifted, allowing the needle tip to be recaptured in the imaging window [Figure 3.5(i)]. Similarly, with the needle being further inserted, the body of the metallic needle gradually appears in the imaging window, as shown from Figure 3.5(j) to 3.5(n). More detailed needle activities captured by the handheld photoacoustic 3D imager are available online (<https://www.researchgate.net/publication/331319683>).

Note that though the handheld imager is moved to another position with a different FOV, z -coordinate information still denotes the absolute depth, referenced by the PDMS-tissue interface. From Figure 3.5(b) to Figure 3.5(i), an insertion distance of 2.1 mm in the z direction is observed.

Figure 3.6 Characterization of imaging resolution for the developed 3D imager. (a) Volume rendered image; (b-d) 2D projected images along the (b) y direction, (c) x direction, and (d) z direction. (e) FWHM analysis.

To quantitatively characterize the imaging resolution, the signal amplitudes along the marked lines in Figure 3.6(b-d) are analyzed. Since the metallic needle is not parallel to the horizontal plane, FWHM could be calculated using a geometrical projection $FWHM = 1/\sqrt{1/x\text{-FWHM}^2 + 1/y\text{-FWHM}^2 + 1/z\text{-FWHM}^2}$, in which $x\text{-FWHM}$, $y\text{-FWHM}$ and $z\text{-FWHM}$ represent the FWHM values projected on x -axis, y -axis, and z -axis, respectively. In this way, FWHM of the needle image is calculated to be about 1.04 mm, with $x\text{-FWHM}$, $y\text{-FWHM}$, and $z\text{-FWHM}$ being measured to be 3.25, 1.89, and 1.37 mm, respectively [Figure 3.6(e)]. Excluding the actual diameter of the metallic needle (0.3 mm), the effective resolution is about 0.74 mm, which is slightly larger than that obtained in the k -wave simulation (0.69 mm horizontally and 0.54 mm axially).

SNR is defined as the ratio of the maximal photoacoustic intensity to the average noise intensity. SNR is measured to be higher than 13 dB with an imaging depth deeper than 5 mm. Overwhelmed by the strong photoacoustic signal from the metallic

needle, the contrast information on background tissues (*e.g.* blood vessel, lipid) is highly suppressed and not discernable.

These experimental results demonstrate the ability of the developed 3D handheld imager to monitor the dynamics of the needle insertion with high imaging contrast, good spatial resolution, and high flexibility. A key advantage of the designed 3D photoacoustic imager is its handheld-operating capability, which enables the user to manually move the handheld probe to any ROI for tracking dynamic activities, especially for imaging moving target. In this way, the 3D handheld imager is operated like the commercially B-mode ultrasound scanner (though in 2D) to capture the 3D dynamic images at several different positions with equivalent wider and flexible FOV.

3.4.2 Handheld photoacoustics guided thermal therapy and temperature monitoring

Photothermal therapy is a noninvasive technique for cancer therapy, in which continuous wave (CW) therapeutic lasers and photoabsorbers (*e.g.* nanoparticles, dyes) are typically employed for continuous heating of cancer cells [175]. To avoid overheating to the surrounding healthy tissue, photoacoustic imaging has been used to monitor the localized temperature variation so that the heat deposition can be precisely monitored both temporally and spatially.

In this *in-vitro* demonstration, IR-820 near-infrared dye [176] is employed as the strong photoabsorber for efficient heat deposition. IR-820 is commercially available and exhibits the peak absorption at 819 nm. Before the photothermal therapy and thermal imaging, the presence and the spatial location of IR-820 in 3D space are first identified using the handheld photoacoustic 3D imager. At the start position [Figure 3.7(a)], although the presence of IR-820 is roughly visible, obtained 3D photoacoustic

images suffer severe artifacts and a low imaging SNR (< 10 dB). This is because the IR-820 is not entirely falling into the imager's FOV and shows a limited photoacoustic efficiency. Benefiting by the handheld capability of the 3D imager, the position of the handheld probe is fine-tuned to target an optimized FOV [from Figure 3.7(a) to 3.7(c)], where the IR-820 is shifted to the center of the FOV, as shown in Figure 3.7(d). The photoabsorbers distribution and the maximal photoacoustic amplitude in Figure 3.7(c) would be employed as the baseline to characterize the temperature elevation in subsequent thermal images. Note that a trajectory of needle injection can be roughly observed in Figure 3.7(a-c), which is due to the contamination of the IR-820 in the process of particle delivery. All the experiments are performed at a room temperature of 25 °C.

Figure 3.7 Handheld photoacoustics guided thermal therapy and temperature monitoring. (a-d) 3D photoacoustic imaging with handheld operation. (e-k) 3D photoacoustic images encoded with temperature elevation. (l) Tendency of the temperature variation.

The photothermal process is performed by using a CW laser diode (5 W, 808 nm) to irradiate the ROI in the porcine tissue. The CW laser diode is driven by a

customized Howland current source [167], where the current pumping the diode is linearly related to the controlling voltage. Therefore, the CW laser can be easily modulated to satisfy the safety requirement and to peruse a stable temperature elevation (within the linear photoacoustic region [175]). 3D temperature images are computed by firstly differentiating the photoacoustic images obtained during the hyperthermia procedure with the baseline photoacoustic image frame [Figure 3.7(c)]. Further based on the temperature calculation model, where a 51 % increase in the photoacoustic signal amplitude corresponds to a 10 °C increase in the temperature for a water-bearing tissue, changes in the photoacoustic signal amplitude are converted to temperature maps in 3D. Furthermore, a binary mask as in Ref. [175] is employed to eliminate the relatively low temperature elevation in the surrounding biological tissue and the background noise. A series of 3D thermal maps at different time points (30, 60, 90, 120, 150 and 180 s) after the photothermal hyperthermia are shown in Figure 3.7(e-j), where the thermal maps are formed by combining both 3D photoacoustic images (in gray scale) and masked 3D temperature images (in hot scale). Such an experiment is repeated five times and the maximal measured temperature changes at different time points are summarized in Figure 3.7(l). During the first 2 minutes, temperature increases rapidly ($> 6\text{ }^{\circ}\text{C}$). Thereafter, the temperature is gradually saturated at a constant level, indicating a balance of energy transfer between the IR-820 and surrounding tissue. In summary, in the 3-minute photothermal hyperthermia, a maximal temperature elevation of about $7.7\text{ }^{\circ}\text{C}$ is overserved, while the temperature rise of the surrounding tissue is masked out due to the relatively low optical absorption and photoacoustic efficiency.

3.5. Discussion and Conclusion

The developed handheld photoacoustic 3D imager has been demonstrated successfully in capturing 3D dynamic activities with high contrast, good resolution, and flexible handheld operations. Detailed analysis of the system stability, power consumption, and safety issues are discussed as follow:

(1). Stability: For some quantitative applications, the imaging and sensing accuracy is directly determined by the stability of the photoacoustic system. Therefore, system stability is of great importance and must be carefully evaluated. In the developed handheld imager, such stability is mainly dominated by three factors.

Firstly, during laser excitation, the temperature of the laser body would inevitably increase, leading to the variation of the laser energy. To avoid such heating induced uncertainty, a low laser repetition rate (5 Hz) is employed for reliable 3D photoacoustic imaging. Under such a condition, the temperature of the laser body increases only about 0.9 degrees, leading to a small energy decrease of about 3 % [Figure 3.8(a)]. Adding a metallic heat sink, a thermoelectric cooling (TEC) controller, or a cooling fan can improve the temperature immunity of the laser body, whereas at the cost of increasing the weight. The second factor that may affect the system stability is the feeding voltage of the battery. In the process of 3D photoacoustic imaging, feeding voltage from the battery decreased from 12.08 V to 11.63 V within 30 minutes [Figure 3.8(b)]. Correspondingly, the laser energy decreased by 4 %. Employing a more stable battery (*e.g.* miniaturized liquid battery) may help to ameliorate the voltage variation induced instability. Thirdly, the environmental temperature (*e.g.* temperature of the tissue surface) would also affect the transducer

sensitivity, thus affects the system stability. Benefitting by the thermal isolation from the PDMS layer, such an effect is highly suppressed.

Figure 3.8 Estimation of system stability for handheld photoacoustic 3D imager.

(2). Laser power consumption: With a 5 Hz laser repetition rate, averaged power consumed by the optical module is calculated to be about 0.95 W. Supported by a 240 mAh rechargeable lithium-ion polymer battery, the 3D handheld probe can operate for at least three hours theoretically, without changing or recharging the battery.

(3). Safety: For skin exposure, ANSI standards allow a maximum permissible exposure (MPE) of 33.7 mJ/cm^2 for 808 nm laser excitation with a pulse duration of 120 ns [165]. In our imaging system, laser energy below the PDMS layer is measured to be about 1.03 mJ and the laser beam spreads over an area about 0.8 cm^2 . Therefore, the laser fluence is about 1.12 mJ/cm^2 , which is well below the allowed MPE.

The flexibility in tailoring the photonic transmitter and the ultrasonic receiver allows the photoacoustic system to be customized in vastly different scales varying from a sizable imaging system with bulky optical irradiation and ultrasonic detection to a portable system. In this chapter, a handheld photoacoustic 3D imager for diagnostic and therapeutic applications was developed and demonstrated *in-vitro*. By fully integrating the optical module and acoustic module within a single handheld photoacoustic probe, the portable imager enables 3D photoacoustic imaging with a

miniaturized probe size of about $160 \times 64 \times 40 \text{ mm}^3$, which is just slightly larger than a commercial B-mode ultrasound linear array. Compared to the state-of-the-art 3D photoacoustic imaging systems employing spherical/ring-shaped arrays, this system provides a more natural solution for the acoustic coupling problem by using a compact 2D matrix array, facilitating flexible and stable handheld operations. Furthermore, the coaxial illumination design with the PDMS layer enables high-efficiency optical transmission and acoustic acquisition, in contrast to other handheld solutions in which optical excitation is provided on the lateral sides of a linear array and thus most optical energy is deposited outside the imaging plane. Therefore, such a compact design of the photoacoustic 3D imager not only greatly decreases the system size but also enables efficient and relatively uniform photoacoustic detection.

A key advantage of this 3D photoacoustic imager is the great flexibility benefited by the highly miniaturized system size and handheld-operating capability. By controlling the handheld probe to any ROI, the 3D photoacoustic imager can be operated as a commercial B-mode ultrasound scanner for dynamic 3D imaging. With the aim of targeting a high photoacoustic sensitivity and a deep penetration depth, the 2D matrix array with a large aperture size (1 mm) and a relatively low center frequency (2.25 MHz) was custom designed. Therefore, at the current stage, the imaging resolution (0.74 mm) is mainly acoustically limited. In this sense, there is still huge potential for further improving the imaging performance by employing a 2D array with smaller elements and a higher ultrasound frequency.

This work highlights the technological and scientific potential of the handheld photoacoustic technique. To fully realize the clinical translation of 3D handheld photoacoustic imaging, further development will concentrate on system miniaturization, and *in-vivo* demonstration of the handheld imager.

Chapter 4. A Miniaturized Handheld Photoacoustic 3D Imager

In the last chapter, a prototype of handheld photoacoustic imaging has been developed and successfully demonstrated *in-vitro*. However, the imaging probe is still relatively large for practical handheld imaging. On the other hand, the photoacoustic coupling is not optimized, inducing a sacrificed acoustic transmission efficiency and degraded imaging performance. Therefore, improving the handheld imaging platform in the way of miniaturizing the imaging probe, enhancing acoustic transmission efficiency and simplifying the photoacoustic coupling based on our first generation handheld photoacoustic 3D imager becomes the focus of this study. In this chapter, a miniaturized handheld photoacoustic 3D imager, as the second version of the handheld 3D imager, is developed and presented. By replacing the low acoustic impedance polydimethylsiloxane (PDMS) with an acoustically matched delay line layer, simpler photoacoustic coupling and higher acoustic transmission efficiency are available. By separating the main body of the laser excitation with the handheld imaging probe, a highly miniaturized and light-weight handheld imaging probe is obtained. Optical Monte Carlo simulation and acoustic *k*-wave simulation are performed to confirm a relatively homogenous photoacoustic sensitivity distribution within a wide field of view (larger than $10 \times 10 \times 10 \text{ mm}^3$). Imaging resolution characterized by imaging two hairs is estimated to be about 0.80 mm in the lateral direction and 0.73 mm in the axial direction. To demonstrate the handheld capability in real-time, photoacoustic imaging guided needle biopsy in the rat's abdomen is performed at a frame rate of about 10 Hz. Mean imaging contrast-to-noise ratio (CNR) is about 14.3 dB and the sidelobe level is about -10.4 dB . Besides, handheld imaging is also demonstrated in visualizing vasculature (mainly cephalic vein) in the

human arm (CNR > 4.1 dB). Such a compact handheld design may promote the clinical translation of the photoacoustic technique.

4.1. Introduction

Taking advantage of the rich optical contrast and deep acoustic penetration in biological tissues, the photoacoustic technique has been demonstrated as a powerful biomedical imaging method. Over the past decade, owing to the great advances in the laser technology and ultrasonic detection technology, the frontier of the photoacoustic technique is expanded dramatically, in the aspects ultrafast imaging [177], super-resolution imaging [178], whole-body imaging [179], multi-spectral functional imaging [180], *etc.*

In this work, based on our previous work on the handheld photoacoustic 3D imager [139], we propose a more miniaturized and practical solution for 3D handheld imaging by employing the fiber-coupled laser excitation and a bio-compatible photoacoustic coupling layer. In the developed handheld probe, optical illumination is provided by a portable fiber laser system, while volumetric acoustic detection relies on the central-holed 2D matrix transducer array. Since piezoelectric materials are opaque, the hole at the center of the aperture works as an optical window, allowing focused laser illumination to pass through the 2D matrix array without any attenuation. Coupled with the lens group (lens and collimator), the bio-compatible photoacoustic coupling layer is placed below the 2D matrix array for light beam expansion, as an optical diffuser. Meanwhile, such a photoacoustic coupling layer also acts as an acoustic delay line to compensate for the incomplete aperture induced sensitivity inhomogeneity, ensuring a relatively homogenous acoustic sensitivity distribution. All the above optical elements and acoustic elements are coaxially assembled into a

compact handheld probe with a weight of 44 g. The utility of the developed handheld photoacoustic imager is demonstrated in: 1) photoacoustic sensitivity simulation, 2) imaging hairs immersed in scattered water for resolution characterization, 3) tracking needle insertion during *in-vivo* needle biopsy, and 4) imaging human arm vasculature with flexible handheld operations.

4.2. Handheld Photoacoustic System Design

4.2.1 Handheld probe design

The developed handheld photoacoustic probe is shown in Figure 4.1(a) and its detailed configuration is illustrated in Figure 4.1(b). To simultaneously satisfy the high-energy requirement for 3D imaging and the miniaturization requirement for handheld imaging, a 15-mJ fiber-coupled laser system (CNI LASER, China) is custom designed. The laser head is about $27 \times 8 \times 6 \text{ cm}^3$ in size and 2 kg in weight. The mechanical coupling between the high-energy fiber (core diameter: 1000 μm ; NA: 0.22 in air) and the internal laser body is firm enough to tolerate moderate movement. This is especially significant for the handheld imaging system that requires frequent handheld operation during the imaging process. The pulsed energy is 10.7 mJ at the tip of the fiber output.

Figure 4.1 (a) Photograph of the developed miniaturized handheld photoacoustic 3D imager. (b) Schematic drawing of the handheld probe.

In the developed handheld imager, the high energy fiber, a fiber collimator, a micro condenser lens, a 2D matrix array and an optical diffuser & acoustic delay line (OD&ADL) constitute the whole handheld probe. To facilitate a compact probe design, these five elements are tightly and coaxially assembled. Uniquely, the 2D matrix array is designed to have a small optical opening ($\varnothing$: 2 mm) at the center of the array aperture for light transmission.

Figure 4.2 (a) Schematic diagram of the light propagation within the handheld probe. (b) Geometric arrangement of the central-holed 2D matrix array.

A schematic diagram of the laser light propagation is illustrated in Figure 4.2(a). In detail, the output laser beam from the fiber is first collimated by a fiber collimator (F220SMA-C-1310, Thorlabs, USA; NA : 0.23 in air). Before passing through the optical opening ($\varnothing$: 2 mm), the quasi-collimated light is converged by a micro condenser lens (PCX-6-6, Edmund, USA; $\varnothing$: 6 mm, f : 6 mm). The back focusing length of the condenser lens is 4.6 mm. To avoid light blocking, the focusing point is located at around 1 mm below the upper surface of the 2D matrix array, while 2 mm above the lower surface. After passing through the central-holed 2D matrix array, the diverging light enters a 7 mm optical diffusing pad, which is fabricated by mixing

optically transparent polyacrylamide gel with predetermined amounts of optical scatters. With the help of such a diffusing pad, the complicated degenerate optical pattern is reformed to be a relatively homogenous fluence profile in a wide imaging field of view (FOV).

The photoacoustic signals are acquired by the above-mentioned custom-designed 2D matrix array (DOPPLER, China) [139]. It contains 72 piezoelectric elements, which are arranged on a 9×9 mesh grids, while nine elements occupying the central 3×3 mesh grids are mechanically removed. The active aperture is about 0.6 mm in diameter and the interval of adjacent elements is 1.07 mm. The central frequency is 2.25 MHz with a bandwidth of about 65 %. The difference in acoustic sensitivity among each element is less than 1.5 dB. Besides the unique optical-opening design, a key advantage of such a customized 2D matrix array is its compactness and thinness. Compared to the bulk PZT transducers used in the previously reported handheld systems [2], the slim design (thickness: 3 mm) of the 2D matrix array greatly promotes the miniaturization of the imaging probe and improves its handheld capability. In addition, a thinner thickness contributes to a shorter distance of optical pathway, facilitating easier light transmission, especially for the wide-angle diverging light in the handheld photoacoustic probe.

Another key acoustic element in the handheld photoacoustic probe is the OD&ADL pad. Optically, it serves as an optical diffuser to generate a relatively uniform optical fluence map; Acoustically, it provides an acoustic delay line for the central-holed 2D matrix array, giving rise to a relatively homogenous acoustic beam pattern. In general, this custom-made photoacoustic coupling layer plays a role of OD&ADL, contributing to a high-efficiency and high-homogeneity photoacoustic

sensitivity in the imaging FOV. Quantitative analysis of the photoacoustic sensitivity pattern will be presented in Section II-B.

Altogether, this handheld photoacoustic probe is developed based on a coaxial design, where all the optical components (laser fiber, collimator, condenser, diffuser) and the acoustic components (2D matrix array, acoustic delay line) are vertically aligned to enable high-efficiency photoacoustic imaging in 3D space. The compact volume of the total handheld probe is less than 10 cm^3 and the weight is about 44 g.

4.2.2 Photoacoustic sensitivity distribution

Figure 4.3 (a) Simulated optical fluence map in the x - z plane. (b) Schematic of the photoacoustic overlap. (c) Simulated acoustic sensitivity distribution in the x - z plane. (d) Simulated optical fluence map in the x - y plane. (e) Simulated photoacoustic sensitivity distribution. (f) Simulated acoustic sensitivity distribution in the x - y plane.

To target an optimized imaging performance of the handheld probe, both optical field simulation and acoustic field simulation are performed. Such simulated optical

field and acoustic field distributions are essential to evaluate the efficiency and effectiveness of the developed handheld photoacoustic imager.

3D fluence map within the region of interest (ROI) is estimated through the Monte Carlo simulation using the Monte Carlo eXtreme (MCX) package [166]. Firstly, the illumination pattern of the laser output is measured by translating a masked energy meter (ES111C, Thorlabs, USA) [79]. The measured optical energy distribution combined with the cone-shaped source type is used as the initial condition in the Monte Carlo process. Complying with the schematic shown in Figure 4.3(b), the light source is generated in the air layer and focused at 2 mm above the array-OD&ADL interface. A semi-infinite medium ($12 \times 12 \times 20 \text{ mm}^3$) with an isotropic 0.2 mm sub-voxel is established. A total of 10^6 photons are launched and the fluence map at the time of 1 ns is computed. Major optical parameters of the OD&ADL used for simulation are given as refractive index n : 1.21, absorption coefficient μ_a : $< 1e^{-5} \text{ mm}^{-1}$, scattering coefficient μ'_s : $1e^{-1} \text{ mm}^{-1}$. Other optical parameters of air and biological tissue used for simulation are the same as those in Ref. [166].

Simulated results are given in Figure 4.3(a) and 4.3(d), where Figure 4.3(a) showcases the fluence map at the x - z cross section ($y = 0 \text{ mm}$) and Figure 4.3(d) showcases the fluence map at the probe-tissue interface ($z = 7 \text{ mm}$). It is worth noting that the cone-shaped diverging light is highly scattered and diffused within the OD&ADL layer. This produced a relatively homogenous circular illumination pattern with a radius of 7 mm, corresponding to the FMHM of about 14 mm. The maximal difference of optical fluency in the $10 \times 10 \times 10 \text{ mm}^3$ region [white window in Figure 4.3(d), set as FOV] is less than 3.2 dB.

The theoretical beam profile of the 2D matrix array in 3D space is obtained with the use of *k*-wave acoustic simulation [119], in which a 3D meshing grid with a domain size of $12.8 \times 12.8 \times 19.2 \text{ mm}^3$ is established. A perfectly matched layer (PML) is created to satisfy the acoustic boundary condition. A 2D planar aperture is created at the center of the simulation volume and its acoustic properties (including center frequency, element size, pitch, apodization, *etc.*) are designed to coincide with that of the actual 2D matrix array employed in the handheld probe. $120 \times 120 \times 180$ point-like sensors are employed as the ideal point detector to record the time-varying pressure field. Major acoustic parameters of the OD&ADL are provided by the manufacturer, as density $\rho_{OD\&ADL}$: 1031 kg/m^3 , speed of sound $c_{OD\&ADL}$: 1550 m/s , acoustic attenuation $\alpha_{OD\&ADL}$: 0.10 dB/cm . Other acoustic parameters of biological tissues used for simulation are the same as those in Ref. [166]. During the simulation, the 2D planar aperture works in transmitting mode and is driven by a 2.25 MHz tone burst excitation (10 cycles). A map of the resulting root-mean-square (RMS) pressure field is produced as the acoustic sensitivity distribution of the central-holed 2D matrix array.

Figure 4.3(c) shows the simulation results at the *x-z* cross section ($y = 0 \text{ mm}$). Due to the absence of the central 3×3 piezoelectric elements, the sensitivity pattern suffers severe inhomogeneity and several dead zones in the acoustic near field ($< 5 \text{ mm}$). With the help of the OD&ADL, the sensitivity distribution of the 2D matrix array is down shifted and the dead zones are effectively eliminated in the imaging FOV. Acoustic sensitivity distribution at the probe-tissue interface ($z = 7 \text{ mm}$) is illustrated in Figure 4.3(f). Within the FOV [white window in Figure 4.3(f)], the maximum difference of the acoustic sensitivity is estimated to be less than 5.7 dB.

The photoacoustic sensitivity distribution of the developed handheld probe is estimated as the product of the optical fluence map and acoustic beam pattern [134] [139]. Figure 4.3(e) gives the calculated photoacoustic sensitivity distribution within the FOV, shown in the 8 dB dynamic range. Expressly, the variation of photoacoustic sensitivity shows dominance in the axial direction, while the variation in the lateral direction is less than 4 dB in each plane, facilitating faithful image reconstruction and easy time gain compensation (TGC).

4.2.3 Data acquisition and image reconstruction

A portable 128-channel data acquisition system (SonixDAQ, BK Medical, Canada) is employed to transmit the raw data from the 2D matrix array. The SonixDAQ provides an analog amplification with a gain of up to 51 dB. Data digitalization is performed in parallel with a sampling rate of 40 MHz. 72-channel data with 1024 samples and 12-bit resolution are transferred for every frame of the volumetric photoacoustic image. A personal computer (Predator 17, Acer, China) synchronizes the laser irradiation and acoustic data acquisition by programming a micro-controller unit (MCU, Arduino, Italy).

Figure 4.4 (a) Photograph of the whole portable photoacoustic system. (b) Acoustic reconstructive environment.

As shown in Figure 4.4(a), the handheld volumetric probe, miniaturized fiber-laser system, portable SonixDAQ, and MCU controller constitutes the whole portable photoacoustic imaging system. The overall size is about $25 \times 25 \times 20 \text{ cm}^3$.

To ensure an optimized imaging performance and real-time imaging capability, volumetric image reconstruction is performed using the fast phase shift migration (PSM) method [139]. Before image reconstruction, data interpolation is performed to increase the spatial accuracy. With the given acoustic characteristics of OD&ADL and the imaging environment [ranging from the fat based low-impedance soft tissue ($\rho_{fat} = 911 \text{ kg/m}^3$ and $c_{fat} = 1440 \text{ m/s}$) to the muscle based relatively high-impedance ‘hard’ tissue ($\rho_{muscle} = 1090 \text{ kg/m}^3$ and $c_{muscle} = 1588 \text{ m/s}$), as shown in Figure 4.4(b)], acquired acoustic signals are extrapolated into the imaging FOV with fast speed ($< 30 \text{ ms}$), facilitating the real-time capability ($\sim 10 \text{ Hz}$) for handheld volumetric imaging.

4.3. Imaging Performance Characterization of the Handheld

Photoacoustic Imager

4.3.1 Resolution characterization of the handheld photoacoustic imager

Imaging resolution and CNR are two vital indicators that determine the range of the applications where this developed handheld imager can be applied. In this work, imaging resolutions are characterized by imaging two human hairs, which are immersed in a water tank at different depths (11 mm and 14 mm). Fresh milk is added into the water tank with a solution of 3 % to mimic the biological tissue in terms of optical scattering.

Figure 4.5 Imaging resolution characterization. (a) Volume rendered photoacoustic images of two hairs. (b, d, f) 2D maximum amplitude projections (MAP). (c, e, g) Line spread function (LSF) analysis.

Reconstructed photoacoustics image in a volume rendered view is illustrated in Figure 4.5(a) and its 2D maximum amplitude projections (MAP) are given in Figure 4.5(b). By performing MAP from different depth ranges, images of two human hairs can be separated by the depth information, as shown in Figure 4.5(d, f). The lateral resolution is measured using line spread function (LSF), which is calculated by averaging the perpendicular amplitude lines along with the hair within the white dashed boxes. As depicted in Figure 4.5(e, g), lateral resolutions (-6 dB width) at the depth of 11 mm and 14 mm are estimated to be about 0.79 mm and 0.80 mm, respectively. Similarly, axial resolution is estimated to be 0.72 mm at a depth of 11 mm and 0.74 mm at a depth of 14 mm.

$$\text{CNR of the captured photoacoustic image is calculated by } \text{CNR} = 20 \log \frac{|\bar{S}_i - \bar{S}_b|}{\sqrt{\sigma_b^2}},$$

where $\bar{S}_i$ is the mean brightness value of the imaging target that is manually selected within a 10-voxel line inside the hair image, $\bar{S}_b$ and σ_b^2 represent the mean

brightness value and the variance of the brightness value of the background within a $5 \times 5 \times 5$ - voxel cube outside the hair image. In this way, imaging CNR is calculated to be about 19.4 dB [19.1 ± 0.3 dB (mean $\pm$ standard deviation) at 11 mm depth, 19.6 ± 0.2 dB at 14 mm]. The sidelobe level, calculated by dividing the mean brightness value of the imaging sidelobe [as shown in Figure 4.5(b)] by the mean brightness value of the hair image, is calculated to be -10.4 dB ± 0.5 dB.

4.3.2 Handheld photoacoustics guided *in-vivo* needle biopsy

Handheld photoacoustic imaging of needle insertion is demonstrated on a male rat (13 weeks, ~ 410 g in weight). Before imaging, hair around the region of the abdomen (about 6×6 cm²) is gently removed with a hair removal lotion [Figure 4.6(a)]. An ultrafine medical injection needle (35 Gauge, length: 30 mm) is employed in the needle biopsy and gradually inserted into the rat's abdomen, under the monitoring and guidance of photoacoustic imaging [Figure 4.6(b)]. Optically transparent ultrasound gel (Aquasonic, USA) is applied to facilitate stable acoustic coupling between the probe head (OD&ADL) and the rat's skin. All procedures are approved by the Institutional Animal Care and Use Committee (IACUC), Nanyang Technological University.

Figure 4.6(c) gives an example of the PSM reconstructed photoacoustic image in 3D space, where the brightest rod-like part corresponds to the image of the metallic needle. Meanwhile, with relatively strong optical absorption and high localized optical fluency, the rat's skin also exhibits strong photoacoustic generation. Noted that the reconstructed image suffers a slight image artefact, with an intensity of 5~7 dB lower than that of the metallic needle. Such an artefact is caused by the incomplete data collection induced by the optical opening in the 2D matrix array, which is also observed in Ref. [139]. Since such information (from the skin and artefact) is of less

interest and may interfere with the needle image, signal extrapolation in the PSM method is only performed from 2 mm to 12 mm below the rat's skin.

Figure 4.6 Demonstration of handheld volumetric imaging during *in-vivo* needle biopsy. (a) Photograph of the rat's abdomen, from which the photoacoustic images are captured. (b) Schematic of the handheld operations during photoacoustics guided needle biopsy. (c) An untruncated photoacoustic image in 3D space. (d-e) Selected snapshots of photoacoustic video at different time.

The detailed process of handheld imaging guided needle biopsy is illustrated in Figure 4.6(b), where the photoacoustic probe experiences three-time handheld operations along the needle's insertion direction (location A, B, and C). At the first stage of needle insertion, the handheld probe is placed at the location A. Fitting the curved surface of the rat's abdomen, the handheld probe is slightly left slanted (15~20

degrees). At the start of the needle insertion, only a small tip of the metallic needle can be observed [*e.g.* the image captured at 2.1 s in Figure 4.6(d)]. Since the main body of the metallic needle is still out of the imaging FOV, imaging contrast is to some extent limited. Subsequently, with the metallic needle gradually inserting into the rat's abdomen (0~7 s), the body of the needle falls into the imaging FOV (4.3 and 6.7 s). Notably, though the insertion angle is almost parallel to the horizontal plane (< 5 degrees), the needle's images show a tendency of downward insertion in the imaging coordinate (x_A , y_A , z_A), which is consistent with the positional relationship between the handheld probe and the metallic needle. After 6.7 s, if the metallic needle keeps inserting forward, the needle tip would escape from the effective imaging FOV. Therefore, the handheld probe is handheldly moved to the location B for a change of imaging FOV, which can also be interpreted as an extension of FOV for handheld imaging. At the location B (25~52 s), inasmuch as the probe-skin interface becomes approximately parallel to the horizontal plane, captured needle dynamics is along a horizontal direction in the new imaging coordinate (x_B , y_B , z_B). Similarly, before the needle tip reaching the margin of FOV, a further handheld shift is executed from the location B to the location C. Contrary to the imaging scenario at the location A, the metallic needle is inserted along an obliquely upward direction in the imaging coordinated (x_C , y_C , z_C). By clockwise rotating the acquired images along the elevation direction [15~20 degrees, as shown in Figure 4.6(f)], needle insertion direction can be adjusted to be identical with those shown in Figure 4.6(d-e). More detailed needle activities captured by the handheld photoacoustic system are available online (<https://www.researchgate.net/publication/338354761>).

Figure 4.7 (a) Off-line reconstructed synthesized image using three groups of data. (b) Schematic of the synthesized reconstruction. (c-e) 2D maximum amplitude projection (MAP) images.

To provide a clearer visualization of the overall process of needle biopsy, photoacoustic reconstruction using three groups of data (4.3 s at location A, 51.7 s at location B, and 84.8 s at location 3) are off-line proceeded. By calibrating the positional relationship between the three imaging locations (A, B, and C), a synthetic image with an equivalently larger FOV is formed. As shown in Figure 4.7(a), needle images acquired at different time are exactly aligned in a straight line, showing the trajectory of needle insertion from 0 to 95 s. Meanwhile, photoacoustic signals generated from the rat's skin can provide a reference for tracking the needle activity within the rat's abdomen. Such a curved outline of the photoacoustic information agrees well with the abdomen's shape [Figure 4.7(b)]. Notably, two intervals are observed in the synthesized image. This is because the handheld operations are not

spatially continuous along the insertion direction and the synthesized FOV cannot cover needle activities at all positions. By providing more meticulous handheld operation or increasing the imaging FOV, such missing contrast information can be retrieved. In this sense, a wide imaging FOV is particularly significant for a handheld imager, not only reducing the frequency of handheld operations but also contributing to volumetric imaging with improved imaging performances.

2D MAP of the volumetric image along different directions are calculated and given in Figure 4.7(c-e). Full width at half maximum (FWHM) of the amplitude profiles is calculated to be 2.71 ± 0.1 mm in the x direction, 1.33 ± 0.05 mm in the y direction, and 1.44 ± 0.05 mm in the z direction. By performing geometric projection in 3D space, the actual FWHM is calculated to be about 0.92 ± 0.03 mm. With the measured imaging resolution (0.80 mm in the lateral direction and 0.74 mm at a depth of about 14 mm in the axial direction), the size of the metallic needle can be estimated to be about 0.12 ~ 0.18 mm, which agrees well with the real diameter of the used metallic needle (35 Gauge). In the ten selected images (from 4.3 to 84.8 s), the mean CNR is estimated to be about 14.3 ± 2.1 dB.

4.3.3 Handheld photoacoustic imaging of human arm vasculature

Handheld photoacoustic imaging is also demonstrated in imaging human arm vasculature. Differing from the rat's abdomen that contains a 3-5 mm lipid layer beneath the skin ('soft' tissue) [181], vasculature in human arm is mainly surrounded by the muscle based 'hard' tissue (deltoid and deltopectoral groove [182]) with a relatively high acoustic impedance. In this imaging demonstration, handheld imaging is performed on a male arm (age: 28 years), where the handheld probe is handheldly scanned along the cephalic vein, as illustrated in Figure 4.8(a). The white dashed

squares indicate the locations of the imaging window [Figure 4.8(b-e)] and the white arrows correspond to the trajectory of the handheld operation.

Figure 4.8 Demonstration of 3D handheld photoacoustic imaging of human arm vasculature. (a) Diagram of the vasculature in human arm. (b-e) volumetric images of the arm vasculature (including the cephalic vein, accessory cephalic vein, and median cephalic vein).

Firstly, the handheld probe is placed at location (b) and Figure 4.8(b) presents the corresponding imaging results (from 2 ~ 4 mm beneath the skin interface). Benefitting by the high sensitivity of the developed photoacoustic system, the cephalic vein is retrieved with a high CNR (~ 5.1 dB). The diameter of the cephalic vein is estimated to be about 2.0 mm (averaged FWHM: 2.7 mm), which is similar to the anatomical results (1.81 mm in Ref. [183]). Since most of the vein branch and blood capillary are distributed in superficial regions, photoacoustic signals from these vessels may overlap with that from the human skin, showing weak photoacoustic efficiency.

By performing handheld operations along the cephalic vein, the imaging FOV of the handheld probe is upward shifted to the location (c) and (d), as shown in Figure 4.8(a). Near the elbow junction, the cephalic vein empties into two secondary veins — the accessory cephalic vein and the median cephalic vein, which can be visualized in Figure 4.8(c) and 4.8(d). White dashed outlines are added to assist the visualization of

the vasculature. Imaging CNR is measured to be 4.3 dB and 4.1 dB, respectively. With the handheld probe further shifting upwardly, the median cephalic vein disappears, and the accessory cephalic vein occupies the whole imaging FOV (CNR: 4.4 dB), as shown in Figure 4.8(e). Overall, visual comparisons show good agreement between the photograph [Figure 4.8(a)] and reconstructed volumetric images [Figure 4.8(b-e)], demonstrating the utility of the handheld imager to map the human arm vasculature with a high CNR (> 4.1 dB) and sufficient intelligibility.

4.4. Conclusion

In this Chapter, a miniaturized handheld photoacoustic 3D imager (as the second generation handheld 3D imager) has been presented. Benefitting by the central-holed design of the 2D matrix ultrasound array and its thinness feature (3 mm), a compact coaxial photoacoustic design is feasible. In this way, all the optoacoustic components (a high energy fiber, a fiber collimator, a micro condenser lens, a 2D matrix array, and an OD&ADL) can be tightly integrated into a compact handheld probe (~ 44 g). In addition, with miniaturized fiber-based laser system and acoustic acquisition system (SonixDAQ and MCU), portability of the whole photoacoustic system is also achieved ($25 \times 25 \times 20$ cm³).

In the handheld probe, the unique coaxial design for optical illumination and acoustic detection greatly reduces the size of the probe head while keeping high photoacoustic efficiency (CNR ~ 14.3 dB for the metallic needle and CNR > 4.1 dB for the human arm vein). Besides the compactness, a key advantage of the developed handheld volumetric imager is its homogeneous photoacoustic sensitivity pattern and wide imaging FOV (larger than $10 \times 10 \times 10$ mm³). In the view of dynamic (temporarily and spatially) imaging, a wide FOV is particularly significant for

handheld imaging [184]. A larger FOV would facilitate better visualization of imaging targets and reduce the frequency of handheld operations. The developed volumetric handheld imager successfully fills this gap by simultaneously providing the real-time handheld capability and a relatively large imaging FOV. Both *in-vivo* photoacoustics guided needle biopsy and human arm imaging results demonstrated the flexible handheld capability. In particular, by performing multiple-location handheld imaging, a synthesized image with a much broader FOV is also available.

In my opinion, there is still massive potential for further evolving the handheld photoacoustic imaging system by exploring more efficient acoustic detection method. It is noted that there were already a lot of work done in this regard, particularly for increasing the FOV and imaging sensitivity. As a reference, the staring hemispherical arrangement of the photoacoustic system has been proposed [184]. In this way, transducer directionality is modified by a dedicated matching layer, providing a wider FOV for the staring photoacoustic transducer array. We look forward to seeing the wide application of handheld photoacoustic imaging on biomedicine.

Chapter 5. A Portable Photoacoustic Temperature Sensing System

With the aim of developing a wearable photoacoustic 3D imager, a preliminary work—a novel photoacoustics based portable sensor for noninvasive monitoring of blood temperature is developed and presented in this chapter. The optical module (a laser diode with collimation lens) and acoustic module (a ring ultrasound transducer with an optical/acoustic transparent Polydimethylsiloxane coupling layer) of the system are integrated to a compact sensor head with a size like a human thumb. The main body includes the laser driver, data acquisition module, and signal processing module. The overall system size is around $14 \times 8 \times 3 \text{ cm}^3$. Temperature calibration and measurement are demonstrated *in-vivo* to achieve a high accuracy 0.5 degrees, with a fast refreshing speed of 80 Hz. In the future, such a developed photoacoustic temperature sensing device can potentially become a wearable patch imager with further miniaturization of the laser diode and the use of 2D matrix transducer array.

5.1. Introduction

Blood temperature is one of the most important biological parameters that reflects the physiological state of the human body. Even a small change in blood temperature beyond the normal range can cause significant influence on physiological functions, such as change metabolic rates, perturb organ function and cause tissue damage. On the other hand, in some hyperthermia applications like thermotherapy or cryotherapy [185], it is necessary to measure the temperature variation in the region of interest (ROI) for the safe deposition of heat energy. To this end, noninvasive temperature monitoring with real-time capability and high temperature sensitivity (1 °C or better) is in great demand. The most accurate method is to directly stretch a thermocouple or

a thermistor into the ROI. However, it is normally invasive thus generally not preferred and often not feasible.

Non-invasive temperature measurement solutions generally depend on applying different kinds of waves that can penetrate a material, either directly or indirectly, to probe certain physical parameters. Various waves have been used, including mechanical waves (*e.g.* ultrasound), electromagnetic waves (*e.g.* radiofrequency wave, light), and even thermal waves as well, each with their strengths and limitations. Being portable and low cost, diagnostic ultrasound-based methods can penetrate deep into the human body and provide real-time temperature information [186]. However, such a method suffers weak sensitivity to temperature variation thus relatively low measuring accuracy. Magnetic resonance thermometry is currently the golden standard in measuring temperature *in-vivo* owing to its excellent accuracy and good spatial resolution [187]. Unfortunately, it is hindered by its high cost and large size. Infrared thermography allows temperature monitoring in real-time with an accuracy of better than 0.1 Celsius [188]. However, the strong scattering of light within biological tissues precludes it from achieving high-resolution monitoring of temperature at depths (*e.g.* deeper than 0.2 mm).

All the above methods only depend on one specific wave to do the sensing, leaving none of them capable of meeting all the requirements for human blood temperature monitoring. The photoacoustic sensing technique, on the other hand, is a multi-wave method that fuses the advantages of two waves: rich contrast of optical wave and good resolution of ultrasound. Very recently, photoacoustics is proposed for *in-vivo* temperature monitoring due to its high sensitivity. There are now several groups actively developing and applying photoacoustic temperature sensing for various applications like monitoring radiofrequency ablation, high intensity focused

ultrasound therapy [46], *etc.* The reported temperature measurements vary in accuracy and penetration depth, depending on the applications. The temperature in a single cell had been measured with an accuracy of 0.2 degrees Celsius and the temperature for cancer therapy is monitored with an accuracy of 0.16 degrees Celsius without accounting the laser energy fluctuations [175]. Even better, it was reported that an improved temperature sensitivity of 0.15 degrees Celsius was obtained in a 2 seconds temporal resolution [141]. Thus, in the aspects of high accuracy and scalable penetration depth, the photoacoustic technique is particularly suited for probing temperature. The advantage and potential of photoacoustic sensing are demonstrated as its system complexity, power consumption and accuracy can be tailored to meet the requirements for different applications.

In this work, to meet the stated challenging needs for noninvasive temperature measurement, we proposed to develop a novel photoacoustics based wearable device, which includes two main parts: a main body and a sensor head. The sensor transmitter (optical module) and receiver (acoustic module) are integrated into a compact sensor head. And the miniaturized main body plays the role of laser intensity modulation, photoacoustic signal collection, amplification, digitization, processing, and overall power management. Results from the phantoms and *in-vivo* animal verification demonstrate the ability of the developed photoacoustic sensor to monitor the temperature variation accordingly.

5.2. Theory of Photoacoustic Temperature Measurement

Photoacoustic effect refers to sound wave generation from an optically absorbing material via thermoelastic mechanism. The material absorbs part of the laser energy and undergoes thermal expansion, launching therefore acoustic waves that could be

detected by an external ultrasound transducer. Under thermal confinement and stress confinement, the photoacoustic pressure can be derived as:

$$p = \Gamma \cdot \mu_a \cdot F, \quad (5.1)$$

where μ_a is the absorption coefficient, F is the laser fluence, Γ is the Grueneisen parameter, which can be expressed as:

$$\Gamma = \frac{\beta c^2}{C_p} = f(T), \quad (5.2)$$

where c is the sound velocity and C_p denotes the specific heat capacity at a constant pressure. As the only term that is temperature dependent, the Grueneisen parameter is linearly proportional to the temperature in the range from 10°C to 55°C [175] and therefore can be simply modeled as:

$$T = \frac{p}{p_0} \left(\frac{A}{B} + T_0 \right) - \frac{A}{B}, \quad (5.3)$$

in which p_0 is the photoacoustic signal amplitude at a baseline-temperature T_0 . After pre-calibration of the material-related parameters A and B , the measured photoacoustic pressure signal can be used to retrieve the temperature.

5.3. System Design

The flexibility in tailoring the photonic and ultrasonic modules allows the sensor to be customized in vastly different scales varying from a huge imaging system with a high-power pulsed laser and ultrasonic array implementation to a portable or even wearable sensor system with a compact continuous wave (CW) laser diode and single element transducer. The overall block diagram of the proposed photoacoustic

temperature sensing device is illustrated in Figure 5.1, including the main body and the miniaturized sensor head. Such an assembly requires only the tiny patchable sensor head to be attached tightly onto the human body (at the neck or close to the chest) to receive photoacoustic signals while the main body can be carried in other parts of the body that can endure the weight.

Figure 5.1 Schematic of the proposed photoacoustic sensing device for blood temperature measurement. (a) Main body. (b) Sensor head. (c) Measurement timing. (d) Photograph of wearable device.

5.3.1 Optical module design

The optical module, including three CW laser diodes and a collimation lens, plays the role of the transmitter in the whole photoacoustic sensor probe. The compact laser diodes working at three wavelengths (808 nm, 650 nm and, 450 nm) are used as the light source, which targets different penetration depths. Falling into the human body window, the near infrared wavelengths (808 nm) allows deep penetration and a higher

irradiation power up to 300 mW/cm² can be used, according to the ANSI safety standard [165]. Whereas, the visible laser diodes (650 nm and 450 nm) target to measure the temperature of the superficial blood vessel due to high absorbing ability but shallow penetration depth in the human tissue.

5.3.2 Acoustic module design

As the counterpart of the optical module, the acoustic module (including a compact ring transducer and a thin transparent photoacoustic delaying layer) acts as the receiver of the whole photoacoustic sensor. A compact 1 MHz ring transducer (Doppler, China) with 1 cm outer diameter, 2 mm inner diameter, and 1 cm thickness is placed rightly below the collimator lens coaxially. Therefore, the laser light can be delivered to the monitoring target through the 2 mm-diameter central hole and the 5 mm transparent polydimethylsiloxane (PDMS).

Integrated with the above-mentioned optical module in a 3D-printed frame, the sensor head is estimated to have a height of 4 cm and a patch area about 2 cm², which is similar to the size of the thumb of an adult. The electrical wires and the fiber are wound together to connect with the main body of the device, as illustrated in Figure 5.1(a) and 5.1(b).

5.3.3 Laser driver circuit design

With the aim of radio-frequency modulation of laser diode irradiation, a voltage-controlled current source circuit with high sensitivity and wide bandwidth is needed. As shown in Figure 5.2, the laser diodes are driven by a customized Howland current source [189], where the laser diode current is sensed by differentially measuring the voltage drop across a shunt resistor in series with the laser diodes. Therefore, the current pumping the diode I_{out} is directly proportional to the control voltage V_{in} by

$I_{out} = 1.0V_{in}$. The operating sequence of the photoacoustic sensor is also given in Figure 5.1(c). With a trigger signal that initiates the measurement, the laser diode is driven by the driver circuit to fire consecutively a train of chirp signal at a repetition rate of 1 kHz.

Figure 5.2 Circuit diagram of the laser diode driver.

5.3.4 Data acquisition and temperature readout

In the photoacoustic temperature measurement, a linear chirp signal sweeping from 0.5 MHz to 1.5 MHz within 200 μ s is used, which is provided by a field-programmable gate array (FPGA). After firing of the laser diodes, the generated photoacoustic signal is first amplified by a low noise amplifier (LNA) and then further conditioned by a variable gain amplifier (VGA), followed by a filter to remove the low-frequency baseline oscillations caused by human movements and other vibrations. The filtered signal is sampled by an analog to digital converters (ADC) with a sampling frequency of 5 MHz. Subsequent digital signal processing (DSP) including signal averaging, chirp-based frequency domain correlation, signal amplitude

extraction, and temperature value calculation are executed in the FPGA. A central control unit coordinates the measurement, display, alert and other functionalities.

5.4. Results and Discussion

The photoacoustic temperature measurement is conducted against a K-type thermocouple (accuracy: 0.2 degrees). Briefly, the temperature variation of the sensing target is recorded by the thermocouple and the photoacoustic thermometry simultaneously in both temperature calibration and measurement. By relating the photoacoustic amplitudes to the thermocouple temperature readings, absolute temperature of the sensing target can be obtained by linear extrapolation.

5.4.1 Phantom experiment

In the preliminary phantom demonstration, black tape is chosen as the monitoring target since its high optical absorption and thus a strong photoacoustic effect. In both temperature calibration and measurement, such a monitoring target is immersed in the water tank to provide the acoustic coupling. Temperature is changed by adding hot water into the water tank and allowing it cool down naturally.

Figure 5.3 Temperature measurement on target phantom with linear fitting. (a) Temperature calibration results. (b) Temperature measurement results.

As showed in Figure 5.3(a), the received photoacoustic amplitude is linearly proportional to the ambient temperature variation with a high coefficient of determination in the temperature calibration progress. With the calibrated regression coefficient ($A=10.54$; $B=635.43$), the photoacoustically measured temperature results are illustrated in Figure 5.3(b). For easy comparison, the temperature measured by the thermistor is also given as the horizontal axis. It is interpreted that the sensing accuracy is better than 0.2 degrees.

5.4.2 *In-vivo* experiment

Further demonstration of the temperature measurement is also carried out on the rat's tail. Like that in phantom measurement, the rat's tail is immersed into water for easy manipulation of temperature variation and acoustic coupling. Similarly, the temperature is changed cooling down the surrounding hot water naturally. As showed in Figure 5.4(a), the rat's tail should be carefully placed right below the center of the probe for the exact alignment of the light and blood vessel. As expected, there is a linear relationship between the photoacoustic signal amplitude and the ambient temperature variation. Due to a limited optical absorption coefficient of the rat's blood vessel and high optical attenuation in the rat's skin, the generated photoacoustic amplitude and measurement accuracy (0.5 degrees) is slightly lower than that in the phantom demonstration.

5.4.3 Performance discussion

The capability of real-time monitoring the temperature using the developed photoacoustic sensor has been demonstrated in both phantom and *in-vivo* experiments. Further improvement of the photoacoustic sensor in the aspects of accuracy, energy consumption, safety, and reliability are then addressed.

Figure 5.4 Temperature measurement on the rat's tail. (a) Photography of the sensing implementation. (b) Calibration results. (c) Measurement results.

(1). Accuracy: The accuracy of the photoacoustic temperature measurement is directly determined by the signal-to-noise ratio (SNR) of the captured photoacoustic signals. Signal average can provide greater accuracy but also give rise to a higher power consumption. Thus, a compromise between the power consumption and sensing accuracy must be made. To strike a balance, 10 times average is adopted, which contributes to an accuracy of 0.5 degrees *in-vivo*.

(2). Power consumption: Assuming a pessimistic laser diode efficiency of 30%, the electrical power consumed by the optical module can be calculated to be about 900 mW. The analog front end including LNA, VGA, filter, and ADC is supposed to

dissipate 1600 mW. As a good example of the portable battery, a 3.7 V 1219 mAh rechargeable lithium-ion polymer battery is employed with a total energy of 18.648 kJ. Assuming the measuring interval of 1 second, such a sensor device can operate independently for about 3 months without charging the battery.

(3). Safety: The ANSI safety standards allow a maximum permissible exposure (MPE) of 200 mW/cm² for visible light and of 300 mW/cm² for near infrared wavelengths, which is well larger than the current laser fluency about 100 mW/cm².

(4). Reliability: Currently, the lightweight and compact patch sensor is the only component that needs to be attached onto the measurement site. The sturdy attachment of the sensor by the PDMS coupling layer is still quite robust to the macroscopic movements of the human body. Searching for a more flexible acoustic coupling layer like polymethyl methacrylate (PMMA) would help to improve the sensor reliability.

5.5. Conclusion

In this chapter, we have demonstrated a portable photoacoustic sensor for non-invasive blood temperature measurement. The overall size of the sensing system is only about $14 \times 8 \times 3$ cm³, which is slightly larger than a normal handphone. Both phantom experiments and *in-vivo* trials on rat's tail demonstrate the capability of real-time temperature measurement with a scalable accuracy (0.2 degrees for phantom and 0.5 degrees for rat's tail). In the future, by further improvement of the sensor accuracy and miniaturization of the sensor head (*e.g.* PMUT technology), such a developed photoacoustic temperature sensing device can be potentially wearable for home health monitoring (HHM).

Chapter 6. A Wearable Photoacoustic 3D Imager

Handheld photoacoustic imagers and a portable functional photoacoustic sensor have been developed and successfully demonstrated in Chapter 3, Chapter 4, and Chapter 5. Based on these works, we further develop a wearable photoacoustic 3D imager that is capable of long-term wearable imaging and flexible personalized scanning. By employing the compact continuous wave (CW) laser diodes based optical irradiation and an ultrathin 2D matrix array based photoacoustic detection in the coherent frequency domain, a wearable imaging probe with a size of about $80 \times 25 \times 24 \text{ mm}^3$ and a weight of 21 g is developed. At the backend, a field-programmable gate array (FPGA) controlled Howland current source drives the laser diodes to excite linear frequency modulated optical irradiation. Recorded by a portable multichannel data acquisition system, the generated photoacoustic responses are firstly compressed with the coherent frequency domain photoacoustic method and then extrapolated in the wavenumber-frequency domain for fast image reconstruction. With three-wavelength (450 nm, 638 nm, and 808 nm) laser irradiation, photoacoustic imaging can be operated multispectrally, endowing the developed imager with the functional imaging capability in 3D space. With the imager worn on the human forearm, hemoglobin oxygen saturation level in arm vasculature can be long-term monitored with high stability. When the imager is applied for imaging in a relatively large area (*e.g.* early melanoma detection in the human breast), flexible personalized scanning in a handheld manner can be performed. This work opens the application potential of the photoacoustic technique in a broad range of areas, including personalized healthcare, home health monitoring, and long-term physiologic monitoring.

6.1. Introduction

Optimal treatment of many chronic noncommunicable diseases, such as breast cancer and thyroid cancer, relies on the detection of some warning signs that are indicative of abnormal conditions (*e.g.* hypoxia, angiogenesis, melanoma generation) and timely response in their early stage. To this end, developing a personalized medical imaging system focusing on early detection of carcinogenesis, early diagnosis, and early treatment is of tremendous interest to researchers and healthcare pioneers [190]. Typically, the system is installed in the patients' home, allowing better follow-up and continuous monitoring outside the hospital while without affecting the normal life. This requires the miniaturization of the medical imager, portability of the backend hardware and incorporation of fast processing algorithms. The imager head is better if wearable to support comfortable long-term monitoring, or portable to support flexible multisite scanning for easy personalized operation.

For broader applications of the photoacoustic technique, many research groups have been attempting to developing miniaturized photoacoustic platforms, involving portable photoacoustic probe [158], small footprint photoacoustic microscopy [148], handheld photoacoustic probe [2], palm sized photoacoustic unit [192], micro-ultrasound platform [71], fingertip system [193], photoacoustic needle [194], *etc.* Though these works greatly promote the miniaturization of the photoacoustic technique, there is still a vast gap between the state-of-the-art photoacoustic technique and wearable applications. Tang *et al.* proposed a wearable scanning photoacoustic system, which contains four linear scanning servos and a single ultrasound transducer based photoacoustic microscopy [195]. However, due to the limited laser repetition rate and the time-consuming scanning process, it costs more than half an hour to generate a 3D photoacoustic frame ($10 \times 10 \times 12 \text{ mm}^3$). Later, the same group further

developed a wearable 3D tomography system with a three-layer ring-shaped transducer array (3×64 elements) [67]. Nevertheless, the wearable probe is still bulky, with a dimension of about $50 \times 50 \times 60 \text{ mm}^3$ (excluding the fiber bundle and the back-end laser system). Moreover, like the previous version, such a wearable device can be only applied in imaging small spherical objects, such as the head or breast of the small animal.

In this work, we present a miniaturized multispectral photoacoustic imager that can perform wearable 3D imaging of human arm vasculature, and also can work as a handheld scanner for flexible multisite diagnosis. System miniaturization is mainly performed in two aspects. Optically, instead of a high-energy pulsed laser system, compact CW laser diodes driven by an integrated driving circuit system are employed as the irradiation source. Acoustically, an ultrathin 2D matrix array is employed for photoacoustic detection in the coherent frequency domain. Integrating the laser diode based optical irradiation system with the patch 2D matrix array based acoustic detection system in a coaxial manner, a high-sensitivity photoacoustic imager with a size of $80 \times 25 \times 24 \text{ mm}^3$ is developed. The imaging performance of this integrated photoacoustic system was initially characterized in imaging a homemade black dot phantom. For early cancer detection, wearable imaging was conducted multispectrally to estimate the hemoglobin oxygen saturation (SO_2) level in human arm vasculature. Imaging of melanoma in a human breast phantom was followed to assess the practicability of handheld scanning with the developed imager for cancerous diagnosis in the human body.

6.2. System Design and Development

6.2.1 System overview

Figure 6.1 shows the developed miniaturized photoacoustic imager, which tightly integrates the CW laser diodes based optical irradiation system and a central-holed 2D matrix array based acoustic detection system. A dedicated acrylic holder along with the strapping structure is designed for flexible handheld operations and wearable applications. It has a dimension of about $80 \times 25 \times 24 \text{ mm}^3$ and the total weight is around 21 g.

Figure 6.1 (a) Photograph of the wearable photoacoustic 3D imager and its potential applications. (b) Exploded view of the 3D imager. (c) Schematic diagram of light propagation within the 3D imager. (d) Schematic diagram of ultrasonic propagation within the 3D imager.

Figure 6.2 shows the photograph of the overall photoacoustic system, including the integrated laser driving system, the wearable imaging probe, two substitutive laser diodes (with different wavelengths), and an acoustic acquisition system. FPGA inside the integrated laser driving circuit system synchronizes the photoacoustic signal

acquisition with the laser excitation. Captured data is then transferred back to a personal computer (PC) for image reconstruction and displayed in real-time. The overall photoacoustic system has a portable dimension of $25 \times 25 \times 20 \text{ cm}^3$.

6.2.2 Optical module design

In photoacoustic imaging, high resolution and rich contrast can be easily achieved using nanosecond pulsed laser irradiation. But conversely, short pulse duration and corresponding high peak power complicate the design of the laser system, contributing to a bulky system size. Therefore, with the aim of wearable realization of the photoacoustic design, compact CW laser diodes are employed in this work as the irradiation source. To endow the wearable photoacoustic imager with functional imaging capability, three high-power CW laser diodes operating at different wavelengths are incorporated. Detailed specifications of these three laser diodes are listed in Table 6.1, where the maximal power is 3.5 W (450 nm), 2.2 W (638 nm) and 2.0 W (808 nm), respectively.

Figure 6.2 Photograph of the whole photoacoustic imaging system.

The schematic diagram of the optical propagation within the 3D photoacoustic imager is illustrated in Figure 6.1(c). Unlike the erect optical assembly in traditional photoacoustic imaging, a lie-flat assembly with a 90-degree elliptical reflective mirror is designed, which facilitates a low-profile implementation of the photoacoustic imager for potential personalized wearable applications. Another unique optical design within this wearable imager is the optical path at the center of the ultrathin 2D matrix aperture, which allows a straightforward laser excitation on the imaging target without using the off-axis optical design as in most miniaturized photoacoustic probe. Such a coaxial design of optical irradiation contributes to a substantially compact photoacoustic assembly and a relatively homogeneous optical field, as demonstrated in Ref. [139].

Table 6.1 Detailed specification of the laser diodes.

Laser diode (model name)	PLPT9-450D	HL6329HD	M9-808-2000-130
Wavelength (nm)	450	638	808
Maximal power (W)	3.5	2.2	2.0
Packaging	Ø9 mm TO can	Ø9 mm TO can	Ø9 mm TO can
Beam divergence (parallel/perpendicular)	9°/49°	10°/33°	8°/30°
Fluence pattern
Mean fluency per pulse (mJ/cm ²)	1.43	1.03	0.94

In detail, since the beam divergence shows a significant difference in the parallel and perpendicular direction, a cylindrical focusing lens (LJ1310L, Thorlabs, USA) is added before the spherical condenser lens (PCX-6-6, Edmund, USA) for beam shape correction. Subsequently, the generated quasi-collimated light is reflected by an elliptical reflective mirror (PFE05-P01, Thorlabs, USA), and then focused to pass

through the 2D matrix array. Before reaching the imaging objective, the diverged light is further diffused by a 7-mm bio-compatible optical focusing and acoustic delay line (OD&ADL). Benefiting by the coaxial optical transmission design and light diffusion within OD&ADL, relatively homogeneous optical irradiation within the imaging field of view (FOV) is obtained. By scanning a masked laser power meter (S140C, Thorlabs, USA) beneath the imager, optical fluency patterns at the initial imaging plane ($z = 0$) are estimated, which is depicted in Table 6.1 (row 6). Maximal differences of optical fluency in the testing plane are measured to be 1.8 dB (450 nm), 2.3 dB (638 nm), and 2.1 dB (808 nm), respectively.

Figure 6.3 (a) Circuit diagram of the laser driver. (b-c) Photograph and micrograph of the laser driver board.

Compared to the conventional pulsed photoacoustic methodology, though photoacoustic imaging using a CW laser diode is capable of contributing to a miniaturized system size, it inherently suffers a limited signal-to-noise ratio (SNR) and deteriorated the depth resolution [27]. To overcome these problems, we implement the coherent frequency domain photoacoustic technique (or called pulse compression) [55], which employs a relatively long linear frequency modulated (LFM) optical excitation (2 ms), while a cross correlation (CCR) based matched filtering compresses the multichannel photoacoustic pulses before image reconstruction. It has been demonstrated that the optimal LFM bandwidth is about 1.14 times the transducer

bandwidth [196]. In this sense, with the matrix transducer frequency of 2.25 MHz (bandwidth $\sim 67\%$), LFM waveform sweeping from 1.4 MHz to 3.0 MHz is employed for optical excitation. In the developed photoacoustic system, such an LFM waveform is generated using the direct digital synthesizer (DDS) technique, which is implemented in an FPGA (Cyclone II, ALTERA). The FPGA generated voltage is then fed into a voltage controlled current source circuit, which serves as a CW laser driver to modulate the diode irradiation. The basics of this laser driver design is a Howland current pump with a current booster (D44H11G) on the output of an op amp (LT6238). Compared to switching pulse width modulation (PWM) drivers [197], this linear driver circuit is capable of providing a cleaner drive current into the laser diode. The current flowing in the laser diode is controlled by differentially measuring the voltage drop over a shunt resistor in series with the laser diode, which can be controlled by the input voltage. The transaction scale factor $V_{\text{IN}}/I_{\text{OUT}}$ can be easily adjusted by using appropriate resistor values, subject to the relationship $V_{\text{IN}}/I_{\text{OUT}} = (R_2/R_1) \cdot R_{\text{SHUNT}}$ and $R_1 = R_4$, $R_2 = R_3$. To enhance the stability of the driver circuit, a compensation capacitor C is adopted, and its value should be set following with the transaction scale factor and the shunt resistor R_{SHUNT} to keep the driver stable. With good linearity and large bandwidth of the driver circuit, the output optical fluency of the CW laser diode is LFM modulated as well for optimized photoacoustic pulse compression. Photograph of the driver board is shown in Figure 6.3(b), and its micrograph is illustrated in Figure 6.3(c). The total size of the laser driver board is about $12 \times 9 \times 2 \text{ cm}^3$. Measured by the masked laser power meter, the mean optical fluency is measured to be about 0.72 W/cm^2 (450 nm), 0.51 W/cm^2 (638 nm), and 0.47 W/cm^2 (808 nm). Taking account of the 2 ms duration of the LFM

waveform, the deposited laser energy [1.43 mJ/cm² (450 nm), 1.03 mJ/cm² (638 nm), and 0.94 mJ/cm² (808 nm)] is far below the ANSI regulated maximal permeable exposure (20 mJ/cm²) for skin safety.

6.2.3 Acoustic module design

Generated photoacoustic wave is captured by the ultrathin 72-element 2D matrix array (Dopper, China) with a 2.25 MHz center frequency and a 67 % mean frequency bandwidth at -6 dB. The 2D matrix array has a physical dimension of $80 \times 15 \times 3$ mm³ including the connector. All 72 piezoelectric elements are evenly spaced within a 9×9 grid, while the central 3×3 elements ($\varnothing$: 2 mm) are mechanically removed to create an optical opening, by which a compact coaxial design can be realized, as illustrated in Figure 6.1(d). However, due to the incomplete aperture for acoustic detection, the designed 2D matrix array suffers poor sensitivity and homogeneity at the acoustic near field. Owing to the acoustic delay line provided by the OD&ADL, an efficient overlap between optical irradiation and acoustic detection with great homogeneity (< 3 dB) is obtained, facilitating high-sensitivity photoacoustic imaging in 3D space with negligible acoustic distortion. The OA&ADL is designed to share the similar acoustic property with typical biological tissue (density $\rho_{OD\&ADL} = 1031$ kg/m³, speed of sound $c_{OD\&ADL} = 1550$ m/s), ensuring efficient acoustic coupling and low acoustic attenuation. Benefiting by the lie-flat design, the miniaturized photoacoustic imager is about 21 mm in thickness, which includes the cylindrical CW laser diode module (12 mm), ultrathin 2D matrix array (3 mm), OA&ADL pad (7 mm), and additional supporting structure (2 mm). The dimension of the whole imager is about $80 \times 25 \times 24$ mm³ and the total weight is around 21 g. Such a compact and

lightweight design of the photoacoustic imager makes it particularly suitable for wearable imaging that requires the imaging probe patching on the human body.

Figure 6.4 Block diagram of the whole miniaturized photoacoustic imaging system, including the (a) optical assembly, (b) acoustic assembly, and (c) signal processing and image reconstruction chains.

A block diagram of the whole photoacoustic imaging system (including the detailed hardware implementation and signal processing chains) is provided in Figure 6.4. Upon laser irradiation, generated photoacoustic waves are firstly captured by the 72-channel matrix array and subsequently fed into a portable data acquisition system (DAQ, BK Ultrasound, Canada). Within this analog front end (AFE), the analog photoacoustic signal first goes through the low noise amplifier (LNA, 30 dB), the programmable gain amplifier (PGA, 21 dB) and the anti-aliasing filter (AAF), and then goes to the 12-bit ADC (40 MHz sampling rate). The FPGA reads and filters the digitized data and stores the data to the external DDR2 memory (16 GB). Once the preset buffer is full, data is transferred to the PC end (Predator 17, Acer) through USB 2.0 communication, facilitating pseudo real-time imaging with fast speed.

Complete data processing and image reconstruction are accomplished in three steps. First, the CCR based pulse compression is performed using the Fourier transform of the (m, n) th acoustic signal $S_{m,n}(\omega)$ and the Fourier transform of the LFM waveform $R(\omega)$, as:

$$ccr(x, y, t - \tau) = \frac{1}{2\pi} \int EB(\omega) R(\omega) S_{m,n}^*(\omega) e^{i\omega(t-\tau)} d\omega, \quad (6.1)$$

$(m = 1, 2 \dots 9; \quad n = 1, 2 \dots 9)$

where $ccr(x, y, t - \tau)$ is the CCR function of the raw acoustic signal $s_{m,n}(t)$ and $EB(\omega)$ is the Exact-Blackman window for noise suppression [198]. Second, after proper data truncation and volumetric interpolation, field extrapolation is performed in the wavenumber-frequency domain at different imaging depths:

$$CCR(k_x, k_y, z, \omega) = e^{ik_z z} \iiint ccr(x, y, t) e^{-ik_x x} e^{-ik_y y} e^{i\omega t} dx dy dt, \quad (6.2)$$

where k_x and k_y are the wavenumber in the lateral directions, k_z is the wavenumber in the depth direction and can be calculated as $k_z = \left((\omega / c)^2 - k_x^2 - k_y^2 \right)^{-1/2}$. Finally, the extrapolated wave field is transformed back into the space domain by first integration over ω , followed by the inverse Fourier transform over k_x and k_y , as:

$$p(x, y, z) = \iiint CCR(k_x, k_y, z, \omega) e^{ik_x x} e^{ik_y y} dk_x dk_y d\omega. \quad (6.3)$$

The second and third steps sequentially compose the fast phase shift migration (PSM) method for image reconstruction over the imaging ROI. Overall reconstruction time for a $10 \times 10 \times 10 \text{ mm}^3$ data structure is less than 0.05 s. Currently, the developed photoacoustic imager can be operated at a maximal frame rate of 3 Hz, which is mainly limited by the data communication between DAQ memory and PC

memory, as well as the long-time signal average before reconstruction. LFM driving of laser diodes with shorter duration may improve the imaging frame rate, however, at the cost of sacrificing imaging SNR.

6.3. Imaging Performance Characterization of the Wearable

Photoacoustic Imager

6.3.1 Resolution characterization of the wearable photoacoustic imager

Figure 6.5 (a) Spectrums of the raw photoacoustic signals. (b) cross correlation (CCR) results of the raw photoacoustic signals. (c) Reconstructed images of the point testing target. (d) Lateral resolution analysis. (e) Depth resolution analysis.

The imaging resolution and SNR are crucial indicators that ultimately determines the range of the application where this developed photoacoustic system can be applied. In this work, imaging performance characterization is conducted with a home-made testing target, in which a high-absorptive black dot ($\varnothing$: 50 μm) is embedded within an optically transparent polyvinyl chloride plastisol (PVC) plate. The testing target is situated beneath the photoacoustic imager and optically translucent ultrasound gel is applied in between to ensure acoustic coupling.

Figure 6.5(a) depicts the spectrum (from 100 kHz to 5 MHz) of the received photoacoustic signal from a single piezoelectric element (2, 2). Consistent with the broadband spectrum of the driving LFM waveform, the received photoacoustic signals show dominance in the frequency ranging from 1.4 MHz to 3.0 MHz. After the CCR based pulse compression, the original long acoustic signal can be compressed into a narrow peak (less than one microsecond), retrieving the depth information of the photoacoustic source. Conceivably, the delay time of the amplitude peak ($\sim 4\mu\text{s}$) is equal to the acoustic time of flight from the imaging target to the transducer aperture. With this delay time, the generated photoacoustic signal can be separated with the direct interference at 0 delay time. Notably, a small secondary peak can be observed at a delay time of about 11 μs , which corresponds to the reflected downward-propagating photoacoustic from the lower surface of the PVC plate.

SNR, defined as the ratio of the maximal photoacoustic amplitude to the root mean square of the background noise, is calculated to be 12.9 dB (for 450 nm), 11.7 dB (for 638 nm), and 12.4 dB (for 808 nm), respectively. As a rule of thumb, SNR gain introduced by the pulse compression is approximately equal to the square root of the time-bandwidth production (35 dB), enabling the weak photoacoustic response (< -20 dB) to be detectable.

Reconstructed photoacoustic images of the testing target using the PSM method are given in Figure 6.5(c). Paired with the black dot ($\text{SNR} > 24 \text{ dB}$), an imaging artifact can be roughly observed with a degraded image $\text{SNR} (< 10 \text{ dB})$. As before, such an imaging artefact is caused by the rigid boundary condition between the PVC plate and air. Resultantly, the distance between the real image and the ghost is about 10 mm, which is exactly two times the plate thickness (5 mm). Quantitative evaluations on imaging resolution in both lateral and depth directions are given in Figure 6.5(d-e). Solid scatters represent the normalized signal amplitudes [along the colored dashed line in Figure 6.5(c)] and the solid lines represent their Gaussian fitted point spread function (PSF). Imaging resolution of the developed imager can be estimated by averaging the full width at half maximum (FWHM) of the PSF curves using different wavelengths. Here, the lateral resolution is measured to be 0.93 mm (0.89 mm for 450 nm, 0.85 mm for 638 nm, 1.01 mm for 808 nm); depth resolution is measured to be 1.01 mm (1.03 mm for 450 nm, 1.14 mm for 638 nm, 1.04 mm for 808 nm). Such an estimated imaging resolution is slightly larger than the optimum imaging resolution (0.74 mm), which is obtained using pulsed laser [139]. Apparently, imaging resolution of the developed photoacoustic imager is mainly acoustically dependent and shows less variance among different-wavelength laser irradiation.

6.3.2 Wearable imaging of human arm vasculature and SO_2 monitoring

Since tumor progression and angiogenesis require huge amounts of nutrients and oxygen, carcinogenesis is typically associated with hypoxia in the surrounding vasculature system. Therefore, carcinogenesis and malignancy of cancer can be identified with continuous SO_2 monitoring [191]. To verify the utility of the developed photoacoustic system for wearable imaging of vasculature and SO_2

monitoring in the human environment, imaging experiment is performed on a male forearm (age: 22 years).

Figure 6.6 Wearable photoacoustic imaging of arm vasculature with (b) 450 nm laser irradiation, (c) 638 nm laser irradiation, and (d) 808 nm laser irradiation. (e) Arm vasculature distribution within the imaging field. (f) Contour 3D image of the superficial cephalic vein (SO₂ level: 35 %). (g) Contour 3D image of the radial artery (SO₂ level: 72 %). (h) Photoacoustically measured SO₂ level in artery and vein.

During the test, the wearable imaging probe is gently strapped on the forearm with two soft ligatures [Figure 6.6(a)]. By simply substituting the diode tubes, photoacoustic images at different wavelengths can be obtained, as shown in Figure 6.6(b-d). At 450 nm and 808 nm (near the isosbestic point [199]), oxyhemoglobin and deoxyhemoglobin show almost identical molar extinction coefficient. Therefore, as shown in Figure 6.6(b) and 6.6(d), the superficial venous blood vessel and deep arterial blood vessel exhibit observable photoacoustic emission. These photoacoustically reconstructed images agree well with the anatomic structure in arm vasculature [Figure 6.6(e)], where the cephalic vein is located at around 1-2 mm beneath the forearm skin, and the depth of the radial artery is about 4-6 mm [200]. Whereas, at 638-nm wavelength, there is a significant difference in the absorption coefficient (one to two orders [199]) between oxyhemoglobin and deoxyhemoglobin.

As expected, the oxyhemoglobin based deep artery vessel is barely visible in the 638 nm photoacoustic image [Figure 6.6(c)]. Based on the absorption spectrum [198] and linear regression analysis [201], SO_2 level at different positions in 3D space can be estimated. Figure 6.6(f) and 6.6(g) illustrate the contour images of 35 % and 72 % SO_2 level, which correspond to the outline of the cephalic vein and the radial artery, respectively. Since the wearable imager is stably strapped on forearm, relatively long-term monitoring of SO_2 is feasible. Figure 6.6(h) depicts the photoacoustically measured SO_2 levels at two specified points in the cephalic vein and the radial artery, respectively, with a time interval of 2 minutes. The mean SO_2 level is measured to be 28.5 % and 69.1 % for vein and artery, respectively. The temporal variation (standard deviation) is less than ± 5 %.

6.3.3 Handheld scanning of human breast phantom and melanoma detection

Melanoma, one of the most dangerous forms of subcutaneous cancer, has been demonstrated to be highly associated with breast cancer [202]. If melanoma can be found early, the cure rate after the surgical procedure can reach up to 58 % [203]. Hence, the detection of melanoma in its early stage is crucial for optimal treatment.

Besides the wearable applications like SO_2 monitoring, the developed photoacoustic imager supports personalized scanning to detect the melanoma within the human body. Different from the conventional benchtop photoacoustic imaging systems, the miniaturized and lightweight imager provides excellent flexibility in personalized scanning. By easily shifting the compact imaging head to different locations, volume rendered images at various anatomical sites can be obtained with high imaging contrast and resolution. Here, 3D photoacoustic imaging is performed on a custom-made human breast phantom, in which 11 melanin masses (to mimic melanoma) are randomly positioned with a depth ranging from 2 to 7 mm beneath the

breast surface. The detailed process of personalized scanning on the breast phantom is available online (<https://www.researchgate.net/publication/338354873>), where the imager experiences five-time scanning operations. In the beginning, the photoacoustic imager is situated at the position (b) and the corresponding volume rendered image is shown in Figure 6.7(b). Consistent with the positional relationship in the photograph, two photo-absorptive melanin masses (B-I and C-I) are well reconstructed with high imaging SNR (9.7 dB) at $z = 7$ mm and $z = 4$ mm, respectively. It is important to see that only the upper and bottom surfaces of the black masses can be clearly visualized. This is due to the limited view of the 2D matrix array and the speckle-free nature of the planar photoacoustic detection [204]. As the photoacoustic imager shifts from the position (b) to the position (c), the mass B-I escapes from the effective imaging FOV, and the mass C-I shifts to the upper side of the imaging window, as shown in Figure 6.7(c). In addition, the mass D-I enters the imaging volume. Particularly, owing to its small size (comparable to the imaging resolution in the depth direction), a spherical image instead of the mere interface is observed. Benefiting by the lightweight imaging probe and flexible handheld-scanning capability, the imager can be easily shifted to other positions [(d), (e) and (f)], where the masses E-I, E-II, and F-I are photoacoustically captured in succession [Figure 6.7(d-f)].

To facilitate a full-view visualization of the breast phantom, calibrated photoacoustic reconstruction using the above five-group of CCR data [Figure 6.7(b-f)] are off-line processed. With known positional information of the scanning probe, a synthetic image covering all these six black masses is retrieved, which agrees well with the raw distribution in the breast phantom, as shown in Figure 6.7(e). Notably, photoacoustic signals generated from the breast surface shows observable

photoacoustic emission as well. Such a curved profile of photoacoustic signals provides a perfect reference to identify the absolute depth of these black masses.

Figure 6.7 Photograph of the human breast phantom. (b-f) Several snapshots of the photoacoustic video when scanning the melanin masses on a human breast phantom. (g) Synthetic photoacoustic image of six melanin masses.

6.4. Conclusion

In this chapter, we present a miniaturized photoacoustic 3D imager with the use of CW laser irradiation. Integrating the compact CW laser excitation system and an ultrathin 2D matrix ultrasonic array, a wearable imaging probe with a compact size of $80 \times 25 \times 24 \text{ mm}^3$ is successfully developed. Additionally, when photoacoustic imaging is applied to inspecting objects within a relatively large area, this wearable imager can be amenable to perform multisite volumetric diagnosis as a handheld scanner.

To our best knowledge, this is the first attempt to develop a wearable photoacoustic 3D imager that is dedicated to human body healthcare. This 3D photoacoustic imager intends to provide some feasible ideas to solve the problems that exist on the miniaturization of the current photoacoustic technique to promote its practical application. Such a compact and lightweight design of the photoacoustic probe makes it particularly suitable for home based wearable applications that require long-term physiological monitoring (*e.g.* SO_2 monitoring).

A key factor contributing to the portability of the 3D imager is the compact CW laser excitation system (involving miniaturized imager head and the integrated laser driver circuit) and the coherent frequency domain photoacoustic technique. Despite the weak generation of the photoacoustic wave, CCR based pulse compression facilitates a depth-resolved 3D imaging with greatly improved SNR and axial resolution.

Another critical design that makes the developed photoacoustic 3D imager suitable for wearable applications is the ultrathin 2D matrix array. Compared to the bulk piezo-electronic transducers generally used in the 3D photoacoustic imaging

system, its unique slim mechanical design (thickness: 3 mm) and central-holed optical design make a tight assembly of photoacoustics possible. Such a highly integrated photoacoustic design opens the possibility of wearable application of the photoacoustic technique and potential translation towards personalized healthcare.

Chapter 7. Conclusion and Future Work

7.2. Conclusion

In summary, with the aim of clinical translation of photoacoustic technique, this thesis comprehensively investigates the handheld photoacoustics from various aspects, including optical illumination design, acoustic detection design, back-end electronics design, imaging reconstruction algorithm development, probe mechanical design, *etc.* A set of handheld photoacoustic 3D imagers are developed to miniaturize the imaging probe, reduce the system complexity, enhancing the usability, and thus to contribute more practical solutions to handheld photoacoustics. The major contributions of this thesis, as outlined earlier, are summarized as follow:

✚ Development of a novel GPU-accelerated two-dimensional synthetic aperture focusing technique (2D-SAFT) for photoacoustic reconstruction in the planar detection geometry.

✚ Development of a phase shift migration algorithm for fast photoacoustic imaging reconstruction in acoustically layered medium, which is dedicatedly designed for the handheld photoacoustic 3D imager.

✚ Development of an all-in-one handheld photoacoustic 3D imager that is completely water-free, provides homogenous imaging sensitivity in a wide ROI, and supports flexible handheld operations.

✚ Development of a miniaturized handheld photoacoustic 3D imager with a small-footprint and lightweight probe, to enhance the usability of handheld photoacoustic imaging.

✚ Development of a highly portable photoacoustic sensor system for noninvasive temperature measurement *in vivo*.

✚ Development of a wearable photoacoustic 3D imager that supports wearable imaging for long-term medical monitoring and flexible scanning for personalized diagnosis.

7.2. Future Work

Despite the impressive progress of handheld photoacoustics in recent years, we have just barely scratched the surface of developing a mature clinical imaging technique. Towards the clinical applications of handheld photoacoustic imaging, a tremendous amount of effort needs to be paid upon various aspects, such as spatial resolution, temporal resolution, contrast and sensitivity, penetration depth, system stability, usability, *etc.* The perspective of my future work on handheld photoacoustics may concern the following:

✚ **Mechanism — handheld thermoacoustic imaging:** Besides in photoacoustics, the feasibility of handheld imaging can be also explored in its twined technique—thermoacoustics. Using a compact magnetic coil for radio frequency (RF) stimulation [55] and a slim ultrasound transducer for coherent frequency domain thermoacoustic detection [27], such a magnetically mediated thermoacoustic solution may provide a more compact implementation of thermoacoustic imaging, promoting the development of the thermoacoustic technique towards portability.

✚ **Instrument — all-optical handheld photoacoustic imager:** In my opinion, there is still massive potential for further evolving the handheld photoacoustic imaging system by exploring more efficient acoustic detection methods. All-optic photoacoustic imaging may provide an alternative solution for simplifying the photoacoustic system without using the complex acoustic system

and avoiding trivial acoustic coupling [205]. In addition, the development of optically transparent piezoelectric materials [206] may inspire the emergence of true co-axial photoacoustic design in the reflection mode, promoting further miniaturization of the handheld photoacoustic imager.

Application — handheld photoacoustics towards close-loop theranostics: The development of the handheld photoacoustic 3D imager in five dimensions opens the possibility for flexible closed-loop therapy. As a reference, in photothermal therapy, benefiting by the high spatial and temporal resolutions endowed by the developed handheld 3D imager, the photoacoustically measured temperature and accumulated thermal dose can be rapidly feedback to the master personal computer for close-loop control of optical power and therapeutic effect.

I would pen my final words in this thesis by a quote of Queen Elizabeth II, "At its heart engineering is about using science to find creative practical solutions. It's a noble profession."

Author's Publication

Journal papers:

1. **S. Liu**, X. Feng, H. Jin, R. Zhang, Y. Luo, Z. Zheng, F. Gao, and Y. Zheng, "Handheld Photoacoustic Imager for Theranostics in 3D," IEEE Transactions on Medical Imaging, vol. 38, no. 9, pp. 2037–2046, 2019.
2. **S. Liu**, W. Song, X. Liao, T. T. Kim, and Y. Zheng, "Development of handheld volumetric photoacoustic imaging system with a central holed 2D matrix aperture," IEEE Transactions on Biomedical Engineering, 2019. DOI: 10.1109/TBME.2019.2963464.
3. **S. Liu**, K. Tang, X. Feng, H. Jin, F. Gao, and Y. Zheng, "Towards wearable healthcare: a miniaturized 3D imager with coherent frequency domain photoacoustics," IEEE Transactions on Biomedical Circuits and Systems, vol. 13, no. 6, pp. 1417–1424, 2019.
4. H. Jin, R. Zhang, **S. Liu**, and Y. Zheng, "Fast and high-resolution three-dimensional hybrid-domain photoacoustic imaging incorporating analytical-focused transducer beam amplitude," IEEE Transactions on Medical Imaging, vol. 38, no. 12, pp. 2926–2936, 2019.
5. H. Jin, R. Zhang, **S. Liu**, Z. Zheng and Y. Zheng, "A single sensor dual-modality photoacoustic fusion imaging for compensation of light fluence variation," IEEE Transactions on Biomedical Engineering, vol. 66, no. 6, pp. 1810-1813, 2019.
6. **S. Liu**, R. Zhang, Z. Zheng, and Y. Zheng, "Electromagnetic–acoustic sensing for biomedical applications," Sensors, vol. 18, no. 10, p. 3203, 2018.
7. **S. Liu**, X. Feng, F. Gao, H. Jin, R. Zhang, Y. Luo, and Y. Zheng, "GPU-accelerated two-dimensional synthetic aperture focusing for photoacoustic microscopy," APL Photonics, vol. 3, no. 2, p. 026101, 2018.
8. H. Jin, R. Zhang, **S. Liu**, and Y. Zheng, "Passive ultrasound aided acoustic resolution photoacoustic microscopy imaging for layered heterogeneous media," Applied Physics Letters, vol. 113, no. 24, p. 241901, 2018.
9. **S. Liu**, R. Zhang, Y. Luo, and Y. Zheng, "Magnetoacoustic microscopic imaging of

conductive objects and nanoparticles distribution,” Journal of Applied Physics, vol. 122, no. 12, p. 124502, 2017.

10. F. Gao, L. Bai, **S. Liu**, R. Zhang, J. Zhang, X. Feng, Y. Zheng, and Y. Zhao, “Rationally encapsulated gold nanorods improving both linear and nonlinear photoacoustic imaging contrast in vivo,” Nanoscale, vol. 9, no. 1, pp. 79–86, 2017.

Conference Presentations:

11. **S. Liu**, X. Feng, R. Zhang, and Y. Zheng, “Portable photoacoustic system for noninvasive blood temperature measurement,” IEEE International Symposium on Circuits and Systems (ISCAS 2018), Florence, Italy. (**Best Paper Awards**, IEEE CAS Life Science and Biomedical Circuits track)

12. **S. Liu**, K. Tang, H. Jin, R. Zhang, T. T. Kim, and Y. Zheng, “Continuous wave laser excitation based portable optoacoustic imaging system for melanoma detection,” IEEE Biomedical Circuits and Systems Conference (BioCAS 2019), Nara, Japan.

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